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(54) Title: DEAZAPURINE NUCLEOSIDE LIBRARIES AND COMPOUNDS

(57) Abstract: Deazapurine nucleoside analog libraries are prepared in a combinatorial library approach. Particularly preferred compounds and libraries include various 7-deazapurines, 9-deazapurines, and 7-deaza-8-azaguanosine as heterocyclic bases, and it is generally preferred that such nucleosides include a ribofuranose as the sugar moiety. It is further contemplated that compounds generated using contemplated libraries may be useful in the treatment of various conditions, particularly viral infections and neoplastic diseases.

DEAZAPURINE NUCLEOSIDE LIBRARIES AND COMPOUNDS

Priority

This application claims priority to US 60/342,410 filed December 17,2001.

Field of The Invention

The field of the invention is combinatorial nucleoside libraries and related compounds.

Background of The Invention

Nucleosides and related compounds interact with many biological targets, and some nucleoside analogues have been used as antimetabolites for treatment of cancers and viral infections. After entry into the cell, many nucleoside analogues can be phosphorylated to monophosphates by nucleoside kinases, and then further phosphorylated by nucleoside monophosphate kinases and nucleoside diphosphate kinases to give nucleoside triphosphates. Once a nucleoside analogue is converted to its triphosphate inside the cell, it can be incorporated into DNA or RNA. Incorporation of certain unnatural nucleoside analogues into nucleic acid replicates or transcripts can interrupt gene expression by early chain termination, or by interfering with function of the modified nucleic acids. In addition, certain nucleoside analogue triphosphates are very potent, competitive inhibitors of DNA or RNA polymerases, which can significantly reduce the rate at which the natural nucleoside can be incorporated. Many anti-HIV nucleoside analogues fall into this category, including 3'-*C*-azido-3'-deoxythymidine, 2',3'-dideoxycytidine, 2',3'-dideoxyinosine, and 2',3'-didehydro-2',3'-dideoxythymidine.

Various nucleoside analogues can also act in other ways, for example, causing apoptosis of cancer cells and/or modulating immune systems. In addition to nucleoside antimetabolites, a number of nucleoside analogues that show very potent anticancer and antiviral activities act through still other mechanisms. Some well-known nucleoside anticancer drugs are thymidylate synthase inhibitors such as 5-fluorouridine, and adenosine deaminase inhibitors such as 2-chloroadenosine. A well-studied anticancer compound, neplanocin A, is an inhibitor of S-adenosylhomocysteine hydrolase, which shows potent anticancer and antiviral activities.

Deazapurine nucleosides and deazapurine nucleotides have recently gained particular attention due to their wide variety of biological activities, including potent anti-HIV activity (Bergman et al.; Nucleosides Nucleotides 1999 Apr-May;18(4-5):897-8), anti-tumor activity (Ramasamy et al.; J Med Chem 1990 Apr;33(4):1220-5), antimicrobial activity (Sung et al.; Arch Pharm Res 1998 Apr;21(2):187-92), and antiviral activity (Bennet et al.; Arch Pharm Res 1998 Apr;21(2):187-92).

Unfortunately, many of these nucleoside analogues that can inhibit tumor growth or viral infections are also toxic to normal mammalian cells, primarily because these nucleoside analogues lack adequate selectivity between the normal cells and the virus-infected host cells or cancer cells. For this reason many otherwise promising nucleoside analogues fail to become therapeutics in the treatment of various diseases.

Selective inhibition of cancer cells or host cells infected by viruses has been an important subject for some time, and tremendous efforts have been made to search for more selective nucleoside analogues. In general, however, a large pool of nucleoside analogues is thought to be necessary in order to identify highly selective nucleoside analogues. Unfortunately, the classical method of synthesizing nucleosides and nucleotides having desired physiochemical properties, and then screening them individually, takes a significant amount of time to identify a lead molecule. Although thousands of nucleoside analogues were synthesized over the past decades, if both sugar and base modifications are considered, many additional analogues are still waiting to be synthesized.

During the last few years, combinatorial chemistry has been used to generate huge numbers of organic compounds, resulting in large compound libraries. If nucleosides could be made through a combinatorial chemistry approach, a large number of nucleoside analogues could be synthesized within months instead of decades, and large nucleoside libraries could be developed.

A combinatorial chemistry approach to nucleosides may also encourage a focus beyond previously addressed biological targets. For example, in the past nucleoside analogues were usually designed as potential inhibitors of DNA or RNA polymerases and several other enzymes and receptors, including inosine monophosphate dehydrogenase, protein kinases, and adenosine receptors. If a vast number of diversified nucleoside analogues could be created,

their use may be far beyond these previously recognized biological targets, which would open a new era for the use of nucleoside analogues as human therapeutics.

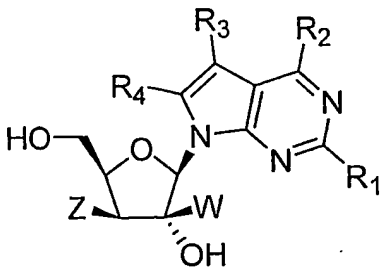
The generation of combinatorial libraries of chemical compounds by employing solid phase synthesis is well known in the art. For example, Geysen, et al. (*Proc. Natl. Acac. Sci. USA*, 3998 (1984)) describes the construction of a multi-amino acid peptide library; Houghton, et al. (*Nature*, 354, 84 (1991)) describes the generation and use of synthetic peptide combinatorial libraries for basic research and drug discovery; and Lam, et al. (*Nature*, 354, 82 (1991)) describes a method of synthesis of linear peptides on a solid support such as polystyrene or polyacrylamide resin.

Although a combinatorial chemistry approach has proven to work well with many types of compounds, there are certain hurdles to the generation of nucleoside libraries. Among numerous other difficulties, most nucleoside analogues contain a sugar moiety and a nucleoside base, which are linked together through a glycosidic bond. The formation of the glycosidic bond can be achieved through a few types of condensation reactions. However, most of the reactions do not give a very good yield of desired products, which may not be suitable to generations of nucleoside libraries. Moreover, the glycosidic bonds in many nucleosides are in labile to acidic condition, and many useful reactions in combinatorial chemistry approaches cannot be used in the generation of nucleoside analogue libraries. As a result, many researchers focused their attention to areas in pharmaceutical chemistry that appear to present easier access to potential therapeutic molecules, and there seems to be a lack of methods for generating libraries of nucleosides and nucleotides using solid phase synthesis. Therefore, there is still a need to provide methods for generation of nucleoside and nucleotide libraries, and especially deazapurine nucleoside and deazapurine nucleotide libraries.

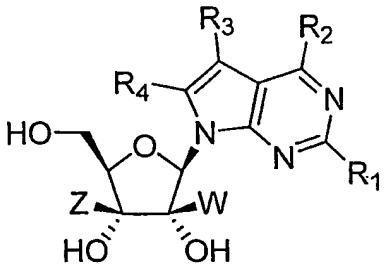
Summary of the Invention

The present invention is directed to synthesis and use of various deazapurine libraries and compounds within those libraries.

In one aspect of the inventive subject matter, a deazapurine library comprises a 7-deaza-purine library that includes compounds according to Formulae 1A and 1B below



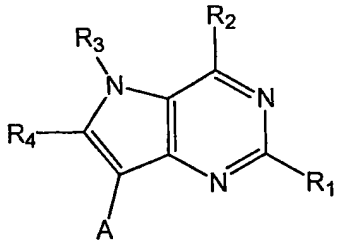
Formula 1A



Formula 1B

wherein W, Z, R_1, R_2, R_3, and R_4 are defined in the respective portions of the detailed description below. Consequently, contemplated nucleosides derived from such libraries will have a corresponding structure according to Formulae 1A and 1B wherein W, Z, R_1, R_2, R_3, and R_4 are also defined in the respective portions of the detailed description below.

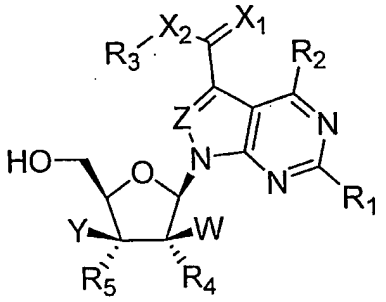
In another aspect of the inventive subject matter, contemplated libraries will include 9-deazapurine-C-nucleosides in which the sugar is covalently bound via the C_1' atom to the 9-carbon atom in the 9-deazapurine base, and contemplated libraries and library compounds will have a structure according to Formula 2



Formula 2

wherein A, R_1, R_2, R_3, and R_4 are defined in the respective portions of the detailed description below. Consequently, contemplated nucleosides derived from such libraries will have a corresponding structure according to Formula 2 wherein A, R_1, R_2, R_3, and R_4 are also defined in the respective portions of the detailed description below.

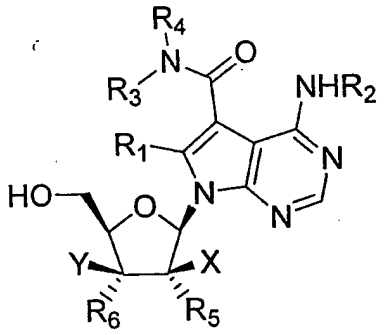
In a still further aspect of the inventive subject matter, contemplated libraries and library compounds include 7-deaza/8-azaguanosine nucleosides and nucleotides according to Formula 3



Formula 3

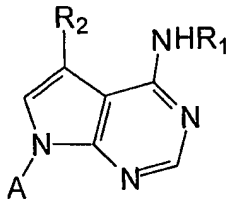
wherein X_1, X_2, W, Y, Z, R_1, R_2, R_3, R_4, and R_5 are defined in the respective portions of the detailed description below. Consequently, contemplated nucleosides derived from such libraries will have a corresponding structure according to Formula 3 wherein X_1, X_2, W, Y, Z, R_1, R_2, R_3, R_4, and R_5 are also defined in the respective portions of the detailed description below.

In yet another aspect of the inventive subject matter, contemplated libraries and library compounds include 7-deazapurine/toyocamycin/sangivamycin nucleosides and nucleotides according to Formula 4A



Formula 4A

wherein X, Y, R_1, R_2, R_3, R_4, R_5, and R_6 are defined in the respective portions of the detailed description below. Consequently, contemplated nucleosides derived from such libraries include molecules having a structure according to Formula 4B wherein A, R_1, and R_2 are also defined in the respective portions of the detailed description below.



Formula 4B

Various objects, features, aspects and advantages of the present invention will become more apparent from the following detailed description of preferred embodiments of the invention.

Detailed Description

The term "nucleoside library" as used herein refers to a plurality of chemically distinct nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs wherein at least some of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs include, or have been synthesized from a common precursor.

For example, a plurality of nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs that were prepared using 1'-azido or 1'-amino ribofuranose as a building block/precursor is considered a nucleoside library under the scope of this definition. Therefore, the term "common precursor" may encompass a starting material in a first step in a synthesis as well as a synthesis intermediate (*i.e.*, a compound derived from a starting material). In another example, at least one step in the synthesis of one of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs is concurrent with at least one step in the synthesis of another one of the nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs, and synthesis is preferably at least partially automated. In contrast, a collection of individually synthesized nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs, and especially a collection of compounds not obtained from a nucleoside library, is not considered a nucleoside library because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs will not have a common precursor, and because such nucleosides, nucleotides, nucleoside analogs, and/or nucleotide analogs are not concurrently produced.

It is further generally contemplated that the complexity of contemplated libraries is at least 20 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs, more

typically at least 100 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs, and most typically at least 1000 distinct nucleosides, nucleotide, nucleoside analogs, and/or nucleotide analogs. Consequently, a typical format of a nucleoside library will include multi-well plates, or a plurality of small volume (*i.e.*, less than 1ml) vessels coupled to each other. The term "library compound" as used herein refers to a nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog within a nucleoside library.

As also used herein, the terms "heterocycle" and "heterocyclic base" are used interchangeably herein and refer to any compound in which a plurality of atoms form a ring via a plurality of covalent bonds, wherein the ring includes at least one atom other than a carbon atom. Particularly contemplated heterocyclic bases include 5- and 6-membered rings with nitrogen, sulfur, or oxygen as the non-carbon atom (*e.g.*, imidazole, pyrrole, triazole, dihydropyrimidine). Further contemplated heterocylces may be fused (*i.e.*, covalently bound) to another ring or heterocycle, and are thus termed "fused heterocycle" or "fused heterocyclic base" as used herein. Especially contemplated fused heterocycles include a 5-membered ring fused to a 6-membered ring (*e.g.*, purine, pyrrolo[2,3-d]pyrimidine), and a 6-membered ring fused to another 6-membered or higher ring (*e.g.*, pyrido[4,5-d]pyrimidine, benzodiazepine). Examples of these and further preferred heterocyclic bases are given below. Still further contemplated heterocyclic bases may be aromatic, or may include one or more double or triple bonds. Moreover, contemplated heterocyclic bases and fused heterocycles may further be substituted in one or more positions (see below).

As further used herein, the term "sugar" refers to all carbohydrates and derivatives thereof, wherein particularly contemplated derivatives include deletion, substitution or addition of a chemical group or atom in the sugar. For example, especially contemplated deletions include 2'-deoxy and/or 3'-deoxy sugars. Especially contemplated substitutions include replacement of the ring-oxygen with sulfur or methylene, or replacement of a hydroxyl group with a halogen, an amino-, sulfhydryl-, or methyl group, and especially contemplated additions include methylene phosphonate groups. Further contemplated sugars also include sugar analogs (*i.e.*, not naturally occurring sugars), and particularly carbocyclic ring systems. The term "carbocyclic ring system" as used herein refers to any molecule in which a plurality of carbon atoms form a ring, and in especially contemplated carbocyclic ring systems the ring is formed from 3, 4, 5, or 6 carbon atoms. Examples of these and further preferred sugars are given below.

The term "nucleoside" refers to all compounds in which a heterocyclic base is covalently coupled to a sugar, and an especially preferred coupling of the nucleoside to the sugar includes a C1'-(glycosidic) bond of a carbon atom in a sugar to a carbon- or heteroatom (typically nitrogen) in the heterocyclic base. The term "nucleoside analog" as used herein refers to all nucleosides in which the sugar is not a ribofuranose and/or in which the heterocyclic base is not a naturally occurring base (*e.g.*, A, G, C, T, I, etc.). Similarly, the term "nucleotide" refers to a nucleoside to which a phosphate group is coupled to the sugar. Likewise, the term "nucleotide analog" refers to a nucleoside analog to which a phosphate group is coupled to the sugar.

It should further be particularly appreciated that the terms nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog also includes all metabolites and/or prodrug forms of a nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog, wherein the prodrug form may be activated/converted to the active drug/nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog in one or more than one step, and wherein the activation/conversion of the prodrug into the active drug/nucleoside, nucleotide, nucleoside analog, and/or nucleotide analog may occur intracellularly or extracellularly (in a single step or multiple steps). Especially contemplated prodrug forms include those that confer a particular specificity towards a diseased or infected cell or organ, and exemplary contemplated prodrug forms are described in "Prodrugs" by Kenneth B. Sloan (Marcel Dekker; ISBN: 0824786297), "Design of Prodrugs" by Hans Bundgaard (ASIN: 044480675X), or in copending US application number 09/594410, filed 06/16/2000, all of which are incorporated by reference herein. Particularly suitable prodrug forms of the above compounds may include a moiety that is covalently coupled to at least one of the C2'-OH, C3'-OH, and C5'-OH, wherein the moiety is preferentially cleaved from the compound in a target cell (*e.g.*, Hepatocyte) or a target organ (*e.g.*, liver). While not limiting to the inventive subject matter it is preferred that cleavage of the prodrug into the active form of the drug is mediated (at least in part) by a cellular enzyme, particularly receptor, transporter and cytochrome-associated enzyme systems (*e.g.*, CYP-system).

Especially contemplated prodrugs comprise a cyclic phosphate, cyclic phosphonate and/or a cyclic phosphoamidates, which are preferentially cleaved in a hepatocyte to produce the compound according to Formula 1 or 2 or their phosphorylated metabolites. There are numerous such prodrugs known in the art, and all of those are considered suitable for use

herein. However, especially contemplated prodrug forms are disclosed in WO 01/47935 (Novel Bisamidate Phosphonate Prodrugs), WO 01/18013 (Prodrugs For Liver Specific Drug Delivery), WO 00/52015 (Novel Phosphorus-Containing Prodrugs), and WO 99/45016 (Novel Prodrugs For Phosphorus-Containing Compounds), all of which are incorporated by reference herein. Consequently, especially suitable prodrug forms include those targeting a hepatocyte or the liver.

Still further particularly preferred prodrugs include those described by Renze et al. in Nucleosides Nucleotides Nucleic Acids 2001 Apr-Jul;20(4-7):931-4, by Balzarini et al. in Mol Pharmacol 2000 Nov;58(5):928-35, or in U.S. Pat. No. 6,312,662 to Erion et al., U.S. Pat. No. 6,271,212 to Chu et al., U.S. Pat. No. 6,207,648 to Chen et al., U.S. Pat. No. 6,166,089 and U.S. Pat. No. 6,077,837 to Kozak, U.S. Pat. No. 5,728,684 to Chen, and published U.S. Application with the number 20020052345 to Erion, all of which are incorporated by reference herein. Alternative contemplated prodrugs include those comprising a phosphate and/or phosphonate non-cyclic ester, and an exemplary collection of suitable prodrugs is described in U.S. Pat. No. 6,339,154 to Shepard et al., U.S. Pat. No. 6,352,991 to Zemlicka et al., and U.S. Pat. No. 6,348,587 to Schinazi et al. Still further particularly contemplated prodrug forms are described in FASEB J. 2000 Sep;14(12):1784-92, Pharm. Res. 1999, Aug 16:8 1179-1185, and Antimicrob Agents Chemother 2000, Mar 44:3 477-483, all of which are incorporated by reference herein.

The terms "alkyl" and "unsubstituted alkyl" are used interchangeably herein and refer to any linear, branched, or cyclic hydrocarbon in which all carbon-carbon bonds are single bonds. The terms "alkenyl" and "unsubstituted alkenyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl with at least one carbon-carbon double bond. Furthermore, the terms "alkynyl" and "unsubstituted alkynyl" are used interchangeably herein and refer to any linear, branched, or cyclic alkyl or alkenyl with at least one carbon-carbon triple bond. The terms "aryl" and "unsubstituted aryl" are used interchangeably herein and refer to any aromatic cyclic alkenyl or alkynyl. The term "alkaryl" is employed where an aryl is covalently bound to an alkyl, alkenyl, or alkynyl.

The term "substituted" as used herein refers to a replacement of an atom or chemical group (*e.g.*, H, NH_2, or OH) with a functional group, and particularly contemplated functional groups include nucleophilic groups (*e.g.*, -NH_2, -OH, -SH, -NC, etc.), electrophilic groups

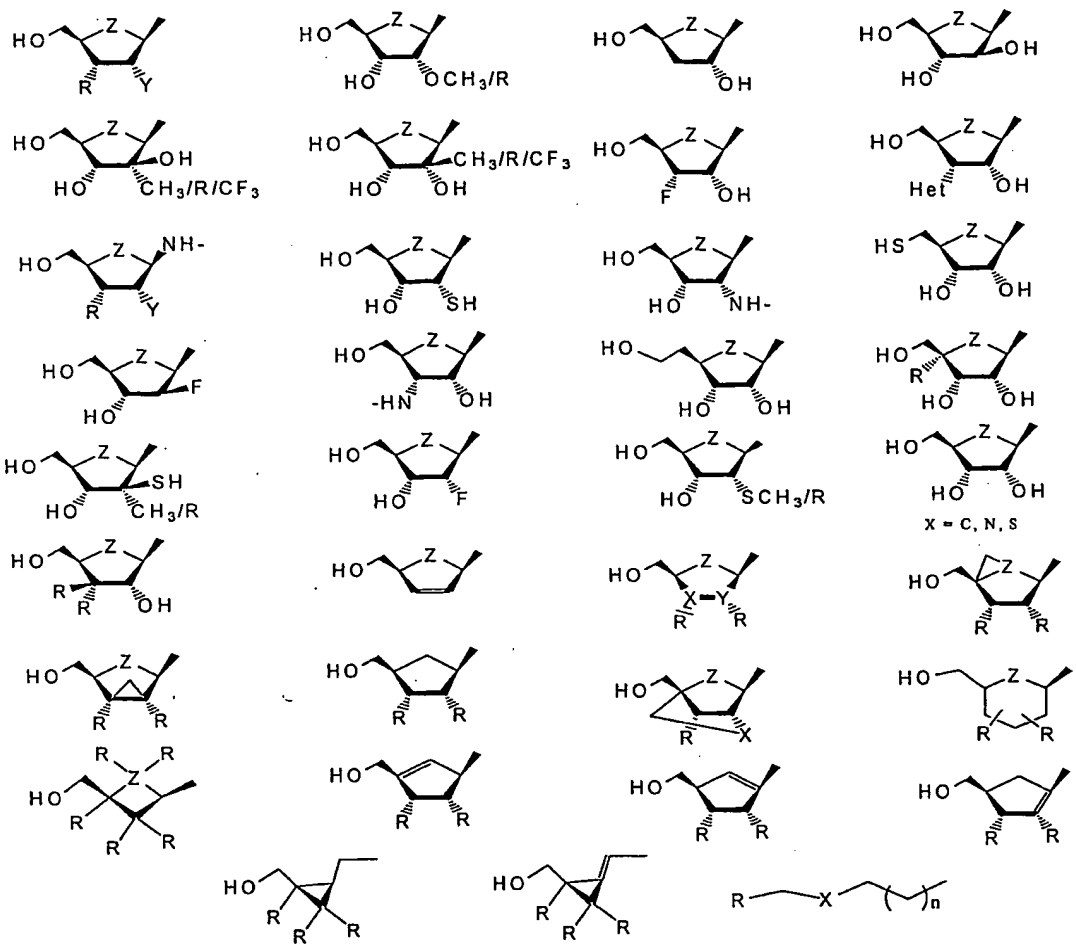
(*e.g.*, C(O)OR, C(X)OH, etc.), polar groups (*e.g.*, -OH), non-polar groups (*e.g.*, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (e.g., $-NH_3^+$), and halogens (e.g., -F, -Cl), and all chemically reasonable combinations thereof. Thus, the term "functional group" as used herein refers to nucleophilic groups (*e.g.*, $-NH_2$, -OH, -SH, -NC, -CN etc.), electrophilic groups (*e.g.*, C(O)OR, C(X)OH, C(Halogen)OR, etc.), polar groups (*e.g.*, -OH), non-polar groups (*e.g.*, aryl, alkyl, alkenyl, alkynyl, etc.), ionic groups (e.g., $-NH_3^+$), and halogens.

Contemplated Sugars

It is contemplated that suitable sugars will have a general formula of $C_nH_{2n}O_n$, wherein n is between 2 and 8, and wherein (where applicable) the sugar is in the D- or L-configuration. Moreover, it should be appreciated that there are numerous equivalent modifications of such sugars known in the art (sugar analogs), and all of such modifications are specifically included herein. For example, some contemplated alternative sugars will include sugars in which the heteroatom in the cyclic portion of the sugar is an atom other than oxygen (*e.g.*, sulfur, carbon, or nitrogen) analogs, while other alternative sugars may not be cyclic but in a linear (open-chain) form. Suitable sugars may also include one or more double bonds.

Still further specifically contemplated alternative sugars include those with one or more non-hydroxyl substituents, and particularly contemplated substituents include mono-, di-, and triphosphates (preferably as C_5' esters), alkyl groups, alkoxygroups, halogens, amino groups and amines, sulfur-containing substituents, etc. It is still further contemplated that all contemplated substituents (hydroxyl substituents and non-hydroxyl substituents) may be directed in alpha or beta position.

Numerous of the contemplated sugars and sugar analogs are commercially available. However, where contemplated sugars are not commercially available, it should be recognized that there are various methods known in the art to synthesize such sugars. For example, suitable protocols can be found in "Modern Methods in Carbohydrate Synthesis" by Shaheer H. Khan (Gordon & Breach Science Pub; ISBN: 3718659212), in U.S. Pat Nos. 4,880,782 and 3,817,982, in WO88/00050, or in EP199,451. An exemplary collection of further contemplated sugars and sugar analogs is depicted below, wherein all of the exemplary sugars may be in D- or L-configuration, and wherein at least one of the substituents (typically H or OH) on the C_1'-C_5' atom of the sugar may be in either alpha or beta orientation.



X, Y, Z = O, S, Se, NH, NR, CH_2, CHR, P(O), P(O)OR
R = H, OH, NHR, halo, CH_2OH, COOH, N_3, alkyl, aryl, alkynyl, heterocycles, OR, SR, $P(O)(OR)_2$ OCOR, NHCOR, $NHSO_2R$, NH_2NH_2, amidine, substituted amidine, quanidine, substituted gyanidine

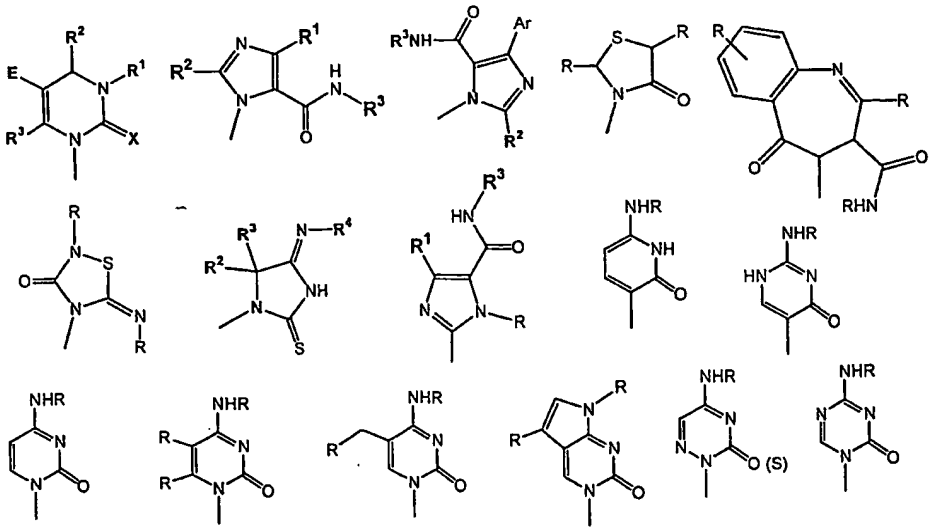
An especially contemplated class of sugars comprises alkylated sugars, wherein one or more alkyl groups (or other substituents, including alkenyl, alkynyl, aryl, halogen, CF_3, CHF_2, CCl_3, $CHCl_2$, N_3, NH_2, etc.) are covalently bound to sugar at the C'_1, C'_2,C'_3,C'_4, or C'_5 atom. In such alkylated sugars, it is especially preferred that the sugar portion comprises a furanose (most preferably a D- or L-ribofuranose), and that at least one of the alkyl groups is a methyl group. Of course, it should be recognized that the alkyl group may or may not be substituted with one or more substituents. One exemplary class of preferred sugars is depicted below:

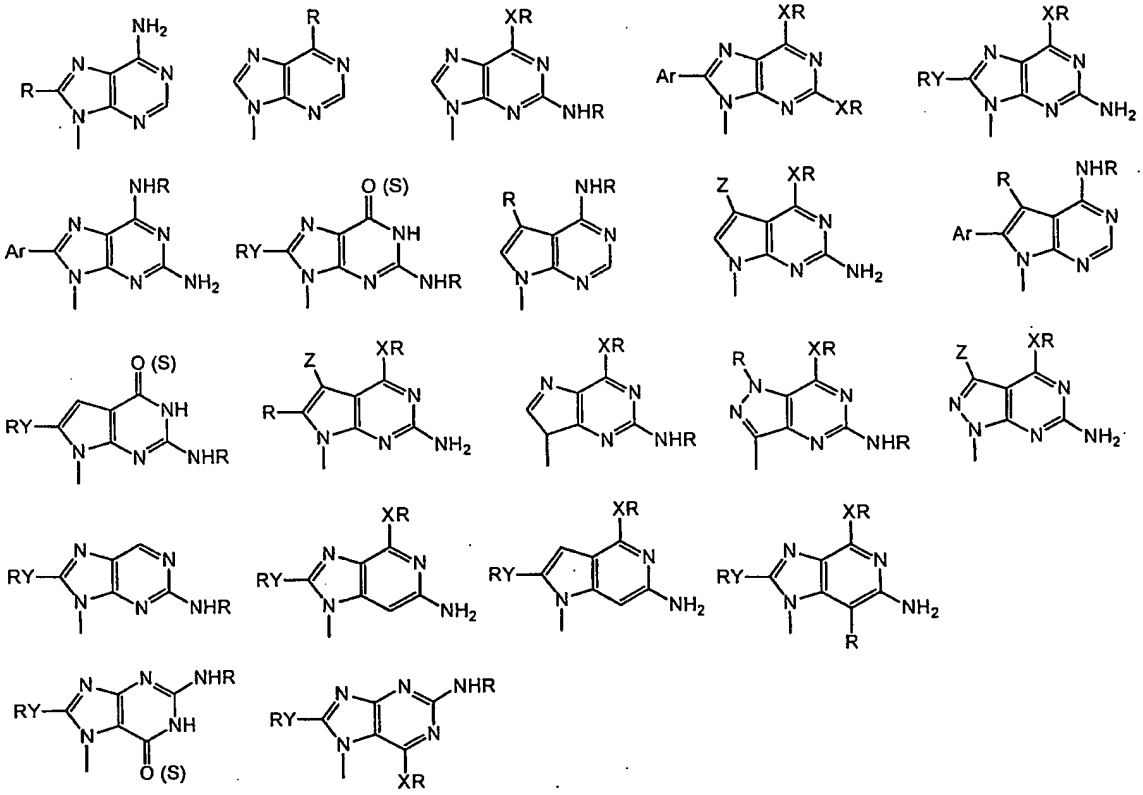
in which B is hydrogen, hydroxyl, or a heterocyclic base, R is independently hydrogen, hydroxyl, substituted or unsubstituted alkyl (branched, linear, or cyclic), with R including between one and twenty carbon atoms.

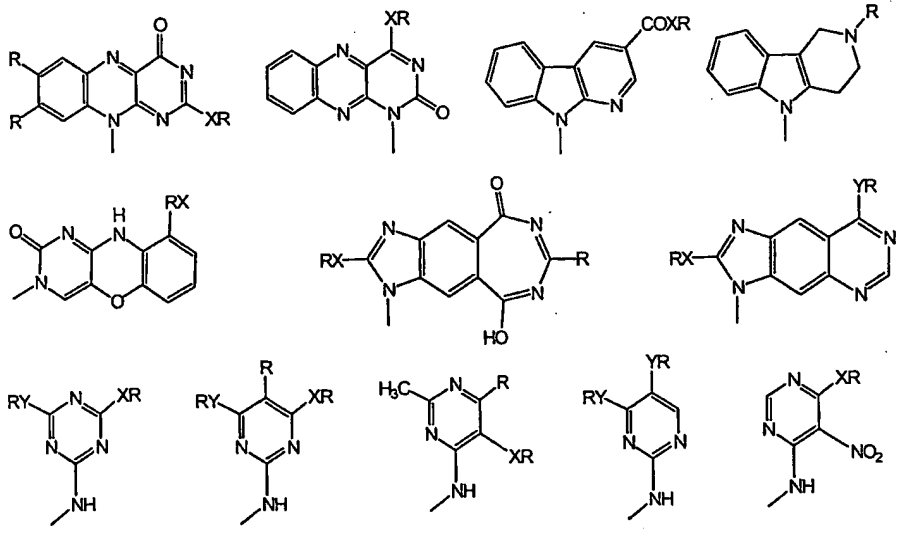
Contemplated Heterocyclic Bases

It is generally contemplated that all compounds in which a plurality of atoms (wherein at least one atom is an atom other than a carbon atom) form a ring via a plurality of covalent bonds are considered a heterocyclic base. However, particularly contemplated heterocyclic bases have between one and three rings, wherein especially preferred rings include 5- and 6-membered rings with nitrogen, sulfur, and/or oxygen as the non-carbon atom (*e.g.*, imidazole, pyrrole, triazole, dihydropyrimidine).

Further contemplated heterocycles may be fused (*i.e.*, covalently bound) to another ring or heterocycle, and are thus termed "fused heterocycle" as used herein. Especially contemplated fused heterocycles include a 5-membered ring fused to a 6-membered ring (*e.g.*, purine, pyrrolo[2,3-d]pyrimidine), and a 6-membered ring fused to another 6-membered or higher ring (*e.g.*, pyrido[4,5-d]pyrimidine, benzodiazepine). An exemplary collection of appropriate heterocyclic bases is depicted below, wherein all of the depicted heterocyclic bases may further include one or more substituents, double and triple bonds, and any chemically reasonable combination thereof. It should also be appreciated that all of the contemplated heterocyclic bases may be coupled to contemplated sugars via a carbon atom or a non-carbon atom in the heterocyclic base.







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Contemplated Solid Phases

It is generally contemplated that all known types of solid phases are suitable for use herein, so long as contemplated nucleosides (or sugar, or heterocyclic base) can be coupled to such solid phases, and so long as the coupled nucleoside (or sugar, or heterocyclic base) will remain coupled to the solid phase during at least one chemical reaction on the nucleoside (or sugar, or heterocyclic base). Especially contemplated solid phases (*i.e.*, solid supports) include Merrifield resins, ArgoGel (available from Argonaut, San Francisco, CA), Sasrin resin (a polystyrene resin available from Bachem Bioscience, Switzerland), TentaGel S AC, TentaGel PHB, or TentaGel S NH_2 resin (polystyrene-polyethylene glycol copolymer resins available from Rappe Polymere, Tubingen, Germany). Alternatively, contemplated solid supports may also include glass, as described in U. S. Pat. No. 5,143,854. Another preferred solid support comprises a "soluble" polymer support, which may be fabricated by copolymerization of polyethylene glycol, polyvinylalcohol, or polyvinylalcohol with polyvinyl pyrrolidine or derivatives thereof (*e.g.*, see Janda and Hyunsoo (1996) *Methods Enzymol.* 267:234-247; Gravert and Janda (1997) *Chemical Reviews* 97:489-509; and Janda and Hyunsoo, PCT publication No. WO 96/03418).

Consequently, it should be recognized that there are numerous methods of coupling nucleosides, sugars, or heterocyclic bases to solid phases that may be appropriate, and a particular method will generally depend on the particular type of solid phase and/or type of sugar. Thus, all of such known methods are contemplated suitable for use herein, and exemplary suitable solid phase coupling reactions are described, for example, in "Organic Synthesis on Solid Phase – Supports, Linkers, Reactions" by Florencio Zaragoza Dorwald et al. John Wiley & Sons; ISBN: 3527299505, or in "Solid-Phase Synthesis and Combinatorial Technologies" by Pierfausto Seneci, John Wiley & Sons; ISBN: 0471331953.

Contemplated Combinatorial Reactions

It is generally contemplated that all known types of combinatorial reactions and/or reaction sequences may be used in conjunction with the teaching presented herein so long as such combinatorial reactions between a substrate and at least two distinct reagents will result in at least two distinct products. Contemplated combinatorial reactions and/or reaction sequences may therefore be performed sequentially, in parallel, or in any chemically reasonable

combination thereof. It is still further contemplated that suitable combinatorial reactions and/or reaction sequences may be performed in a single compartment or multiple compartments. Preferred combinatorial reactions and/or reaction sequences include at least one step in which a substrate or reaction intermediate is coupled to a solid phase (with may include the wall of the reaction compartment or a solid or soluble polymers), and that the solid phase is physically separated from another substrate on another solid phase.

While not limiting to the inventive subject matter, it is generally preferred that contemplated solid phase synthesis is at least partially automated. There are numerous methods and protocols for combinatorial chemistry known in the art, and exemplary suitable protocols and methods are described in "Solid-Phase Synthesis and Combinatorial Technologies" by Pierfausto Seneci (John Wiley & Sons; ISBN: 0471331953) or in "Combinatorial Chemistry and Molecular Diversity in Drug Discovery" by Eric M. Gordon and James F. Kerwin (Wiley-Liss; ISBN: 0471155187).

Contemplated Libraries and Nucleosides

The inventors discovered that nucleoside analog libraries can be prepared in various combinatorial library approaches, including libraries in which protected deazapurine nucleosides are reacted in a sequence of reactions on various positions in the heterocyclic base to obtain a diverse population of molecules. Alternatively, an optionally protected heterocyclic deazapurine base is first reacted with a desired sugar to prepare a particular deazanucleoside or deazanucleotide, which is then reacted in a sequence of reactions on various positions in the heterocyclic base to obtain a diverse population of molecules.

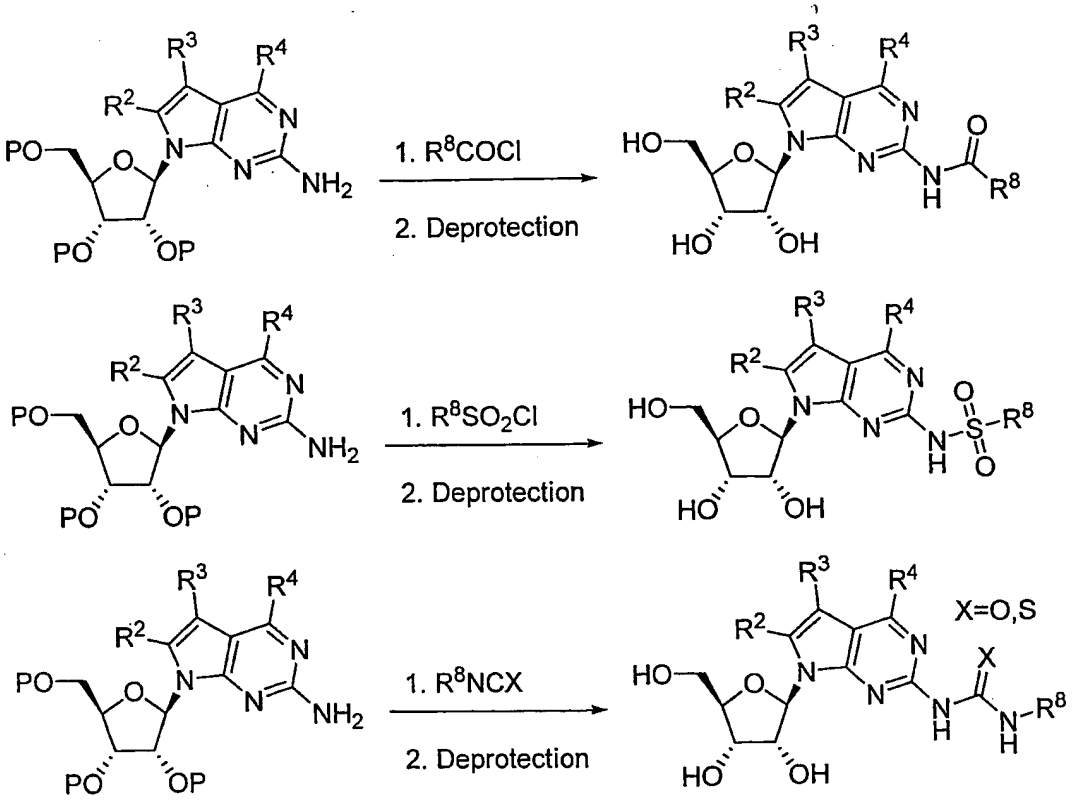
7-Deazapurine Libraries

In a particularly preferred aspect of the inventive subject matter, the inventors have discovered that 7-deazapurine libraries may be produced in a sequence of reactions in which a 7-deazapurine nucleoside has a plurality of substituents R_1, R_2, R_3, and R_4 on the heterocyclic moiety as depicted in **Schemes 1A-D** below.

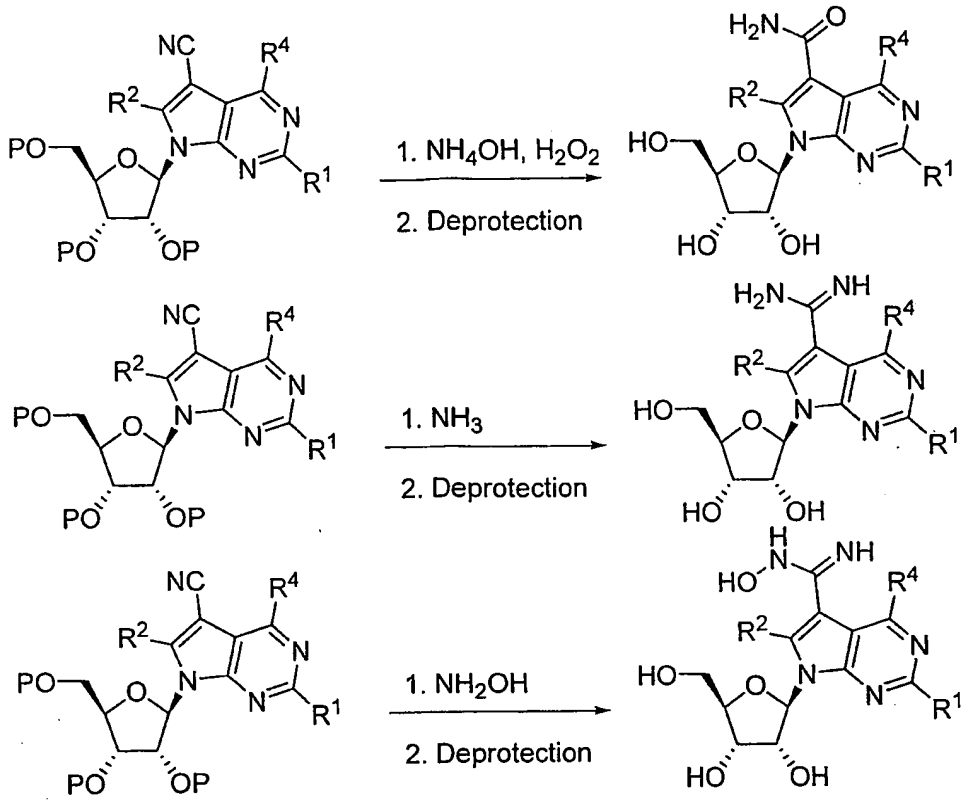
Depending on the chemical nature of the substituents, at least one of the substituents can further be derivatized to a diverse group of secondary substituents in a reaction with a group of reagents as indicated by the arrows below. For example, where the heterocyclic base includes an amino group in the 2-, 6-, 7-, and/or 8-position, it is contemplated that the amino

group can be employed as a nucleophilic reagent with a series of substrates (*e.g.*, a series of activated carboxylic acids to produce a series of secondary substituents -NHCOR, a series of activated sulfonic acids to produce a series of secondary substituents –$NHSO_2R$, etc.) as depicted in **Scheme 1A**. In another example, where R_2 is an azido group, it is contemplated that the azido group may be reacted with numerous nitrogen-containing groups, including an (optionally substituted) amino group and a nitro group.

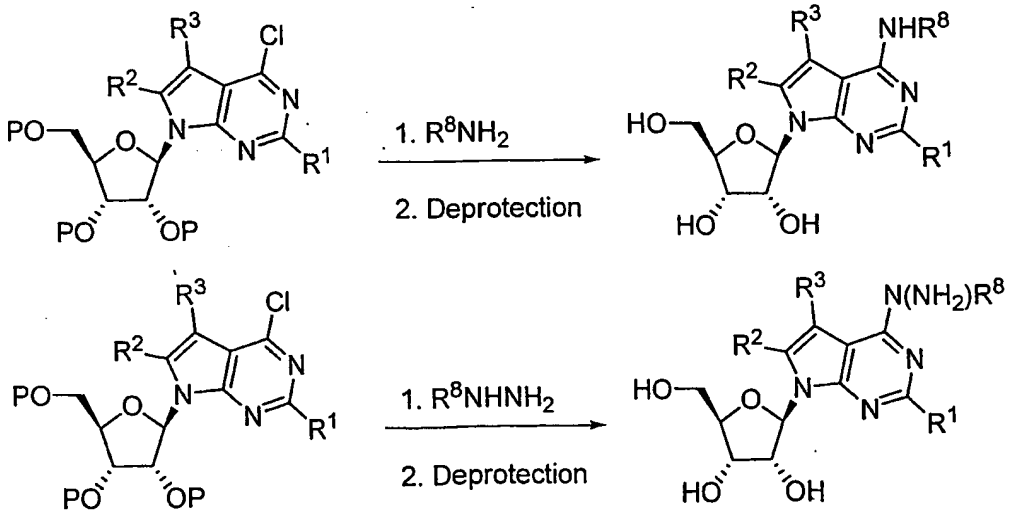
In a still further example, where the R_3 group comprises a CN group, it should be recognized that the CN group may be hydrolyzed/converted into a carboxylic acid group, a primary amine group, or an aldehyde, wherein at least the carboxylic acid group, the primary amine group, and the aldehydes group may still further be derivatized to yield a subsequent set of products as depicted in **Scheme 1B**. In yet further examples, as shown in **Schemes 1C and 1D**, the heterocyclic base has a halogen in the 6- or 8-position. In such compounds, it is contemplated that the halogen may be replaced in a (*e.g.*, nucleophilic aromatic) substitution reaction to generate a plurality of desired products.



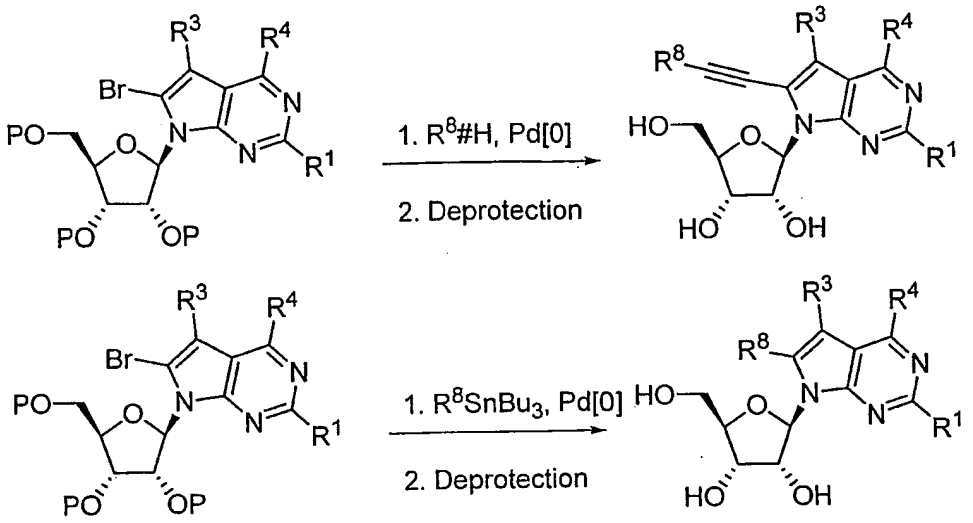
Scheme 1A



Scheme 1B



Scheme 1C



Scheme 1D

With respect to the sugar, it should be appreciated that numerous alternative sugars are also appropriate, and especially contemplated alternative sugars include furanose sugars in which the C_3' substituent is in beta orientation. However, it should be also be recognized that the particular chemical nature of the sugar is not limiting to the inventive subject matter. Therefore, suitable sugars also include sugars with four, five, or six carbon atoms, which further may have numerous substituents other than a hydroxyl group on at least one of the C_2' and C_3' atom. Exemplary contemplated sugars are described and depicted above. Particularly preferred substituents on the C_3' position include hydrogen, N_3, NH_2, OH, SH, or NHR wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

Consequently, the nature of appropriate protection groups for the sugar moiety may vary considerably. While it is particularly contemplated that suitable protection groups include benzyl-, acetyl-, and TBDMS groups, numerous alternative protection groups are also considered suitable. Among other groups, a collection of appropriate alternative protection groups and their reactions is described in Protective Groups in Organic Synthesis by Peter G. M. Wuts, Theodora W. Greene, John Wiley & Sons; ISBN: 0471160199.

Of course it should be recognized that at least some, if not all of such reactions may be carried out while the sugar portion is coupled to a solid phase, and it is further contemplated that the coupling of the sugar may be in any position other than the C_1' position (The radical P in the sugar portion in the C5'-position in Schemes 1A-1D may be a protecting group or a solid

phase, while the radical P in the remaining positions of the sugar is a protecting group). Consequently, it is generally preferred that the coupling of the sugar to the solid phase is via the C_5' atom, however, coupling via the C_2' and C_3' atom are also considered suitable. While coupling of the sugar to the C_4' atom is not excluded, such coupling is less preferred.

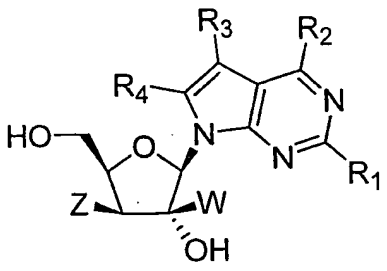
With respect to the solid phase it is contemplated that all known solid phases are suitable for use in conjunction with the teachings presented herein, and exemplary suitable solid phases are described, for example, in Organic Synthesis on Solid Phase – Supports, Linkers, Reactions; by Florencio Zaragoza Dorwald et al. John Wiley & Sons; ISBN: 3527299505, or in Solid-Phase Synthesis and Combinatorial Technologies by Pierfausto Seneci, John Wiley & Sons; ISBN: 0471331953. Preferred solid phases, however, include Merrifield resins, ArgoGel (available from Argonaut, San Francisco, CA), Sasrin resin (a polystyrene resin available from Bachem Bioscience, Switzerland), and TentaGel S AC, TentaGel PHB, or TentaGel S NH_2 resin (polystyrene-polyethylene glycol copolymer resins available from Rappe Polymere, Tubingen, Germany).

There are numerous 7-deazapurine nucleosides known in the art (see *e.g.*, Girgis et al.; J Med Chem 1990 Oct;33(10):2750-5; Seela et al., Nucleosides Nucleotides Nucleic Acids 2000 Jan-Feb;19(1-2):237-51; Guangyi Wang et al. *J. Med. Chem.* 2000 (43) pp 2566-2574; Bheemarao Ugarkar et al. *J. Med. Chem.* 2000 (43) pp 2883-2893; Guity Balow et al. Nucleic Ac. Res. 1998 (26) 3350-3357; Miroslav Bobek and Alexander Bloch, Nucleosides Nucleotides 1994 (13) 429-435; or Sung et al., Arch Pharm Res. 1998 Apr;21(2):187-92) and many of these are commercially available. It should further be appreciated that 7-deazapurine nucleosides may further be modified by introduction of various substituents, and suitable methods for introducing substituents into purine nucleosides are provided in WO90/08147.

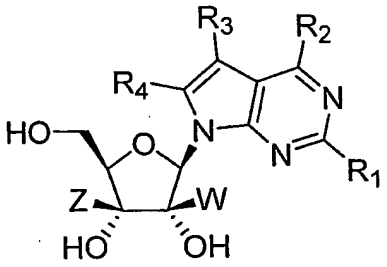
With respect to the derivatization reactions on at least one of the R_1, R_2, R_3, and R_4 substituents, it is contemplated that a particular substituent will typically determine what kind of derivatization may be introduced in a particular position. For example, where the substituent is hydrogen, it is generally contemplated that no further derivatization will occur. On the other hand, where the substituent is N_3 or NH_2, it is contemplated that such substituent may be converted into a substituted amine (-NHR, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl). Further particularly contemplated substituents for R_1-R_4 include halogens, hydroxyl- and thiol

groups, CH_2NH_2, CN groups, and R, wherein R can be an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

Thus, it should be particularly appreciated that all combinations of R_1-R_4 and their derivatives in the deazapurine base will potentially be represented in the so generated library. Moreover, depending on the coupling reaction, the heterocyclic base may be coupled to the nitrogen atom of the heterocyclic base or the carbon atom. After derivatization of at least one of R_1-R_4, it is contemplated that the protecting groups are removed from the sugar moiety (where present), and the sugar is cleaved from the solid phase. Consequently, contemplated compounds may include molecules according to formulae 1A and 1B



Formula 1A



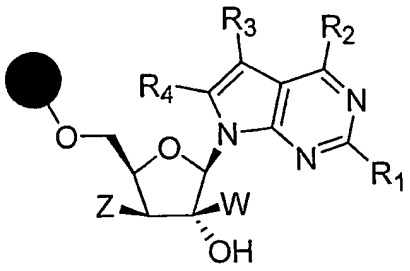
Formula 1B

wherein W and Z are independently hydrogen, N_3, NH_2, OH, SH, R or NHR wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl, and wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Halogen, NH_2, NHR', R', CN, $CONH_2$, N_3, NH_2, and CH_2CN, wherein R' is selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, and an unsubstituted aryl.

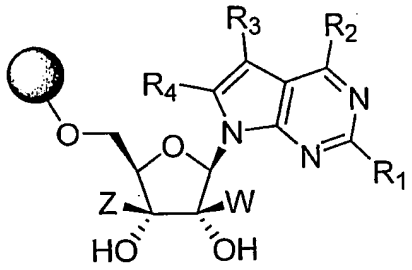
Particularly preferred compounds according to Formulae 1A and 1B include those in which Z is H and W is methyl, or wherein R_1, R_3, and R_4 are independently NHR', wherein R' is selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, and an unsubstituted aryl. In still further preferred compounds R_4 is halogen.

Consequently, it should be recognized that contemplated libraries will include a plurality of compounds according to Formula 1C or Formula 1D, wherein a first compound of the plurality of compounds has a first set of substituents W, Z, R_1, R_2, R_3, and R_4, and wherein

a second compound of the plurality of compounds has a second set of substituents W, Z, R_1, R_2, R_3, and R_4



Formula 1C

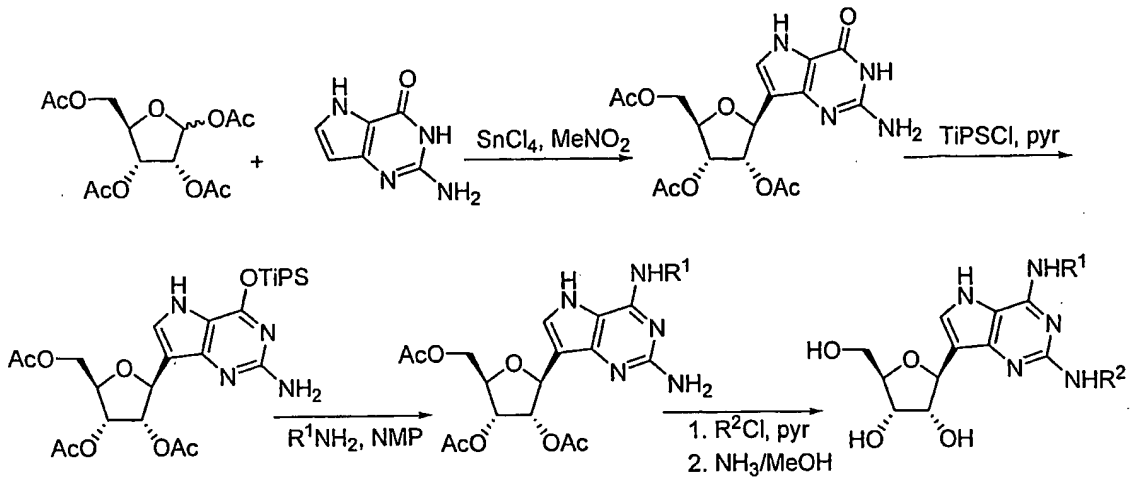


Formula 1D

wherein W and Z are independently hydrogen, N_3, NH_2, OH, SH, R, or NHR wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Halogen, NH_2, NHR', R', CN, $CONH_2$, N_3, NH_2, and CH_2CN, wherein R' is selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, and an unsubstituted aryl; wherein ● comprises a solid phase, and wherein not all of the substituents W, Z, R_1, R_2, R_3, and R_4 in the first set are the same as the substituents W, Z, R_1, R_2, R_3, and R_4 in the second set.

9-Deazapurine C-Nucleosides

The inventors have further discovered that 9-deaza-C-nucleosides can be synthesized by covalently coupling a desired sugar via the C_1' atom of the sugar to the 9-carbon atom in a 9-deazapurine base, and by further modifying the heterocyclic base in one or more reactions to produce a plurality of modified 9-deaza-C-nucleosides. The synthesis generally follows a protocol as depicted in **Scheme 2** below (similar to protocols described in Thomas Cupps *et al. J. Org. Chem.* 1986 (51) 1058-1064, or in Nabih Girgis *et al. J. Med. Chem.* 1990 (33) 2750-2755.



Scheme 2

Here, an appropriate sugar (which is optionally protected and bound to a solid phase) is covalently coupled to a 9-deazapurine, wherein various substituents in the 9-deazapurine system are derivatized in a plurality of subsequent reactions. Depending on the chemical nature of the substituents, at least one of the substituents can further be derivatized to a diverse group of secondary substituents in a reaction with a group of reagents as shown in Scheme 2 above.

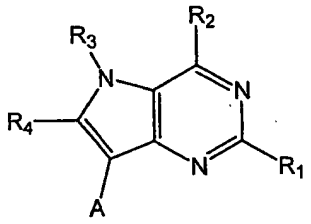
For example, where a substituent is a nucleophilic group (*e.g.*, a NH_2 group), the substituent may be derivatized with a set of diverse electrophilic substrates. In another example, where the substituent is a halogen, it is contemplated that the halogen may be replaced with a nucleophilic reagent in a substitution reaction. In a still further example, where the R_3 group comprises a CN group, it should be recognized that the CN group may be hydrolyzed/converted into a carboxylic acid group, a primary amine group, or an aldehyde, wherein at least the carboxylic acid group, the primary amine group, and the aldehydes group may still further be derivatized to yield a subsequent set of products.

Of course it should be recognized that at least some, if not all of such reactions may be carried out while the sugar portion is coupled to a solid phase, and it is further contemplated that the coupling of the sugar may be in any position other than the C_1' position. Consequently, it is generally preferred that the coupling of the sugar to the solid phase is via the C_5' atom, however, coupling via the C_2' and C_3' atom are also considered suitable. While coupling of the sugar to the C_4' atom is not excluded, such coupling is less preferred.

With respect to the sugar, it is contemplated that all known sugars and sugar analogs are suitable for use in conjunction with the teachings presented herein, and especially preferred sugars include substituted and unsubstituted ribofuranose, and arabinose. Furthermore, all of the contemplated sugars may further include one or more substituents other than hydrogen and hydroxyl in the non-C1' position, and the same considerations for such substituted sugars apply as described above. Moreover, contemplated sugars may advantageously be coupled to a solid phase and be protected as described above.

The formation of the carbon-carbon bond in contemplated nucleosides and nucleotides is well known in the art and will generally follow a protocol as described in Gibson et al. (Nucleosides Nucleotides 1999 Mar;18(3):363-76), Liang et al. (Carbohydr Res 1997 Aug 25;303(1):33-8), or Girgis et al. (J Med Chem. 1990 Oct;33(10):2750-5).

Contemplated reagents for the first derivatization reaction (of Scheme 2) include various nucleophiles, and especially primary amines. Similarly, contemplated reagents for the second derivatization reaction (of Scheme 2) include numerous electrophiles, and particularly acid chlorides, activated esters, anhydrides, etc. Thus, depending on the particular chemical reaction to introduce one or more substituents on the 9-deazapurine, contemplated substituents may include various alkyls, substituted alkyls, alkenyls, substituted alkenyls, aryls, and substituted aryl, but also CHR', NHNHR', NH_2, NHR', or SR', OR', NHR', NHNHR', CH_2CH_2NHR', C(O)R', wherein R' is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl. Consequently, contemplated compounds will have a structure according to Formula 2



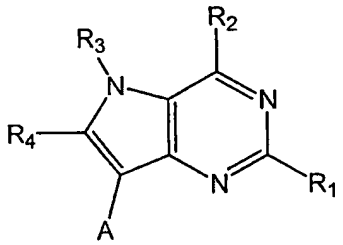
Formula 2

wherein A is a sugar, R_1 is CHR', NHNHR', NH_2, or NHR', R_2 is SR', OR', NHR', NHNHR', CH_2CH_2NHR', or C(O)R', and wherein R_3 and R_4 are independently any one of R',

wherein R' is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl.

Especially preferred compounds according to Formula 2 include those in which the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, wherein the sugar is in a D-configuration or in an L-configuration. Particularly further preferred compounds include those in which R_1 is NHNHR' or NHR', R_2 is NHR', NHNHR', or CH_2CH_2NHR', and wherein R_3 and R_4 are independently R', wherein R' is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl.

Consequently, contemplated libraries may include a plurality of compounds according to Formula 2B wherein a first compound of the plurality of compounds has a first set of substituents A, R_1, R_2, R_3, and R_4, wherein a second compound of the plurality of compounds has a second set of substituents A, R_1, R_2, R_3, and R_4

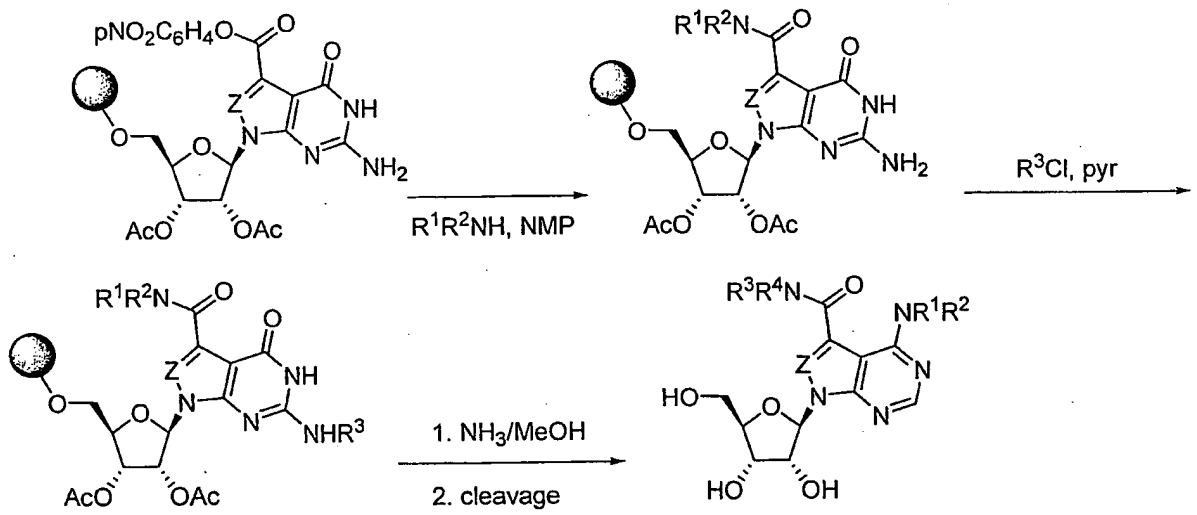


Formula 2B

wherein A is a protected sugar (preferably a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, or arabinose, wherein the sugar may be in D-or L-configuration) that is covalently bound to a solid phase or an unprotected sugar that is covalently bound to a solid phase; R_1 is CHR', NHNHR', NH_2, or NHR', R_2 is SR', OR', NHR', NHNHR', CH_2CH_2NHR', or C(O)R', and wherein R_3 and R_4 are independently R', wherein R' is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl; and wherein not all of the substituents A, R_1, R_2, R_3, and R_4 in the first set are the same as the substituents A, R_1, R_2, R_3, and R_4 in the second set.

7-Deaza/8-Azaguanosine Libraries

The inventors have still further discovered that 7-deaza/8-azaguanosine libraries can be produced by reacting a protected 7-deaza/8-azaguanosine analog with a first set of reagents that replace a first leaving group and subsequently reacting the amino group of the guanosine with a second set of reagents as depicted in **Scheme 3**.



Scheme 3

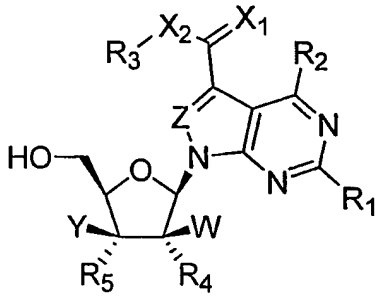
Here, the starting material was obtained by preparing a nitrophenyl-ester from a protected 7-deaza-8-azaguanosine nucleoside, which has been previously coupled to a solid phase using procedures well known in the art. Synthesis of the 7-deaza-8-azaguanosine nucleoside is described in Nucleic Acid Research 1983;11:871-82. Alternatively, 7-deazaguanosine may be employed as the heterocyclic base, and the synthesis of 7-deazaguanosine is described in Tetrahedron Letters 1987;28:5107-5110 and Journal of Heterocyclic Chemistry 1988;25:1893-1898. With respect to suitable sugars, protecting groups, and solid phases (including reactions to couple the sugar to the solid phase), the same considerations as described above apply.

It is further contemplated that the first set of reagents typically includes all reagents that can replace the leaving group from the nitrophenyl-ester, and a particularly preferred first set of reagents include a nitrogen, oxygen, or sulfur atom that act as a nucleophile. For example, a preferred first set of reagents includes RNH_2, $RNHNH_2$, RSO_2NH_2, ROH, RSH, $ROHNH_2$,

$RONH_2$, and RNHOH, wherein R is hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, or a substituted aryl. However, it should be recognized that alternative nucleophiles are also suitable and especially contemplated alternative nucleophiles include thiol reagents and Grignard reagents. There are numerous such first reagents commercially available, and where contemplated first reagents are not commercially available, it should be appreciated that synthesis of such compounds (*e.g.*, various primary amines, alcohols, thiols, etc.) is well known in the art, and exemplary protocols for their synthesis may be found in Advanced Organic Chemistry: Structure and Mechanisms (Part A) by Francis A. Carey, Richard J. Sundberg; Plenum Pub Corp; ISBN: 0306462435; or Advanced Organic Chemistry : Reactions and Synthesis (Part B) by Francis Carey, Richard J. Sundberg; Plenum Pub Corp; ISBN: 0306434571, or Compendium of Organic Synthetic Methods, Volume 9, by Michael B. Smith, John Wiley & Sons; ISBN: 0471145793.

Similarly, the second set of reagents may vary considerably, and it is generally contemplated that all reagents are suitable that react with or without prior activation with the amino group in the deazapurine heterocyclic base. Especially contemplated second sets of reagents include RCOA, RSO_2Cl, RNCO, and RNCS, wherein R is hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, or a substituted aryl. There are numerous such second reagents commercially available, and where contemplated second reagents are not commercially available, it should be appreciated that synthesis of such compounds (*e.g.*, various CoA-esters, thionyl chlorides, isocyanates and isothiocyanates, etc.) is well known in the art, and exemplary protocols for their synthesis may be found in the references given above for the first set of reagents.

Consequently, contemplated compounds may have a structure according to Formula 3



Formula 3

wherein X_1 is NH, NR, O, S, or ONH_2, X_2 is O, S, NH, NHNH, NR, Z is CH or N, Y and W are OH, halogen, alkyl, alkenyl, alkynyl, and wherein R, and R_3 are independently selected from the group consisting of hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl, and wherein R_4 and R_5 are independently selected from the group consisting of hydrogen, halogen, OH, OR, SH, SR, and alkyl and wherein R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, OH, OR, SH, SR, NH_2, NHR and alkyl.

Particularly preferred compounds include those in which R_4 and R_5 are OH, X_2 is O, S, or ONH, Z is CH or N, R_1 is NHCOR, $NHSO_2R$, or NHNHCOR, R_2 is OH, and wherein W and Y are independently selected from the group consisting of hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl (wherein Z is preferably N).

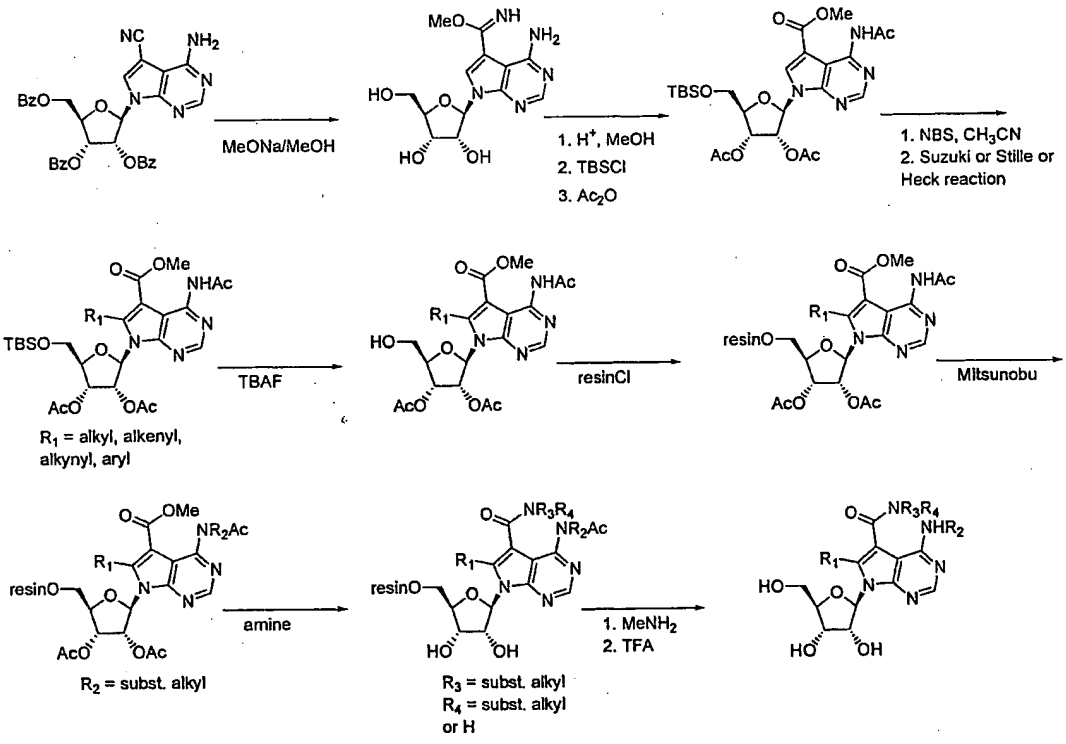
7-Deazapurine/Toyocamycin Libraries

In another aspect of the inventive subject matter, the inventors have discovered that 7-deazapurine/toyocamycin libraries can be produced by derivatizing a 7-deazapurine over several subsequent steps to generate molecular diversity as shown in **Scheme 4A** below. Here, a protected 7-deaza-7-cyano-8-bromoadenosine is reacted with a first set of reagents in a Suzuki, Stille, or Heck reaction to yield the corresponding 8-substituted 7-deazaadenosine derivatives, which are subsequently deprotected. The cyano group is then hydrolyzed to the corresponding carboxylic acid methyl ester, and the nucleoside is coupled to a solid phase (after addition of protecting groups to the sugar portion and amino group of the heterocyclic base). A second set of substituents is coupled to the purine portion using the amino group, and in a further diversification reaction, the ester group on the heterocyclic base is reacted with a substituted or unsubstituted amine to yield the final products.

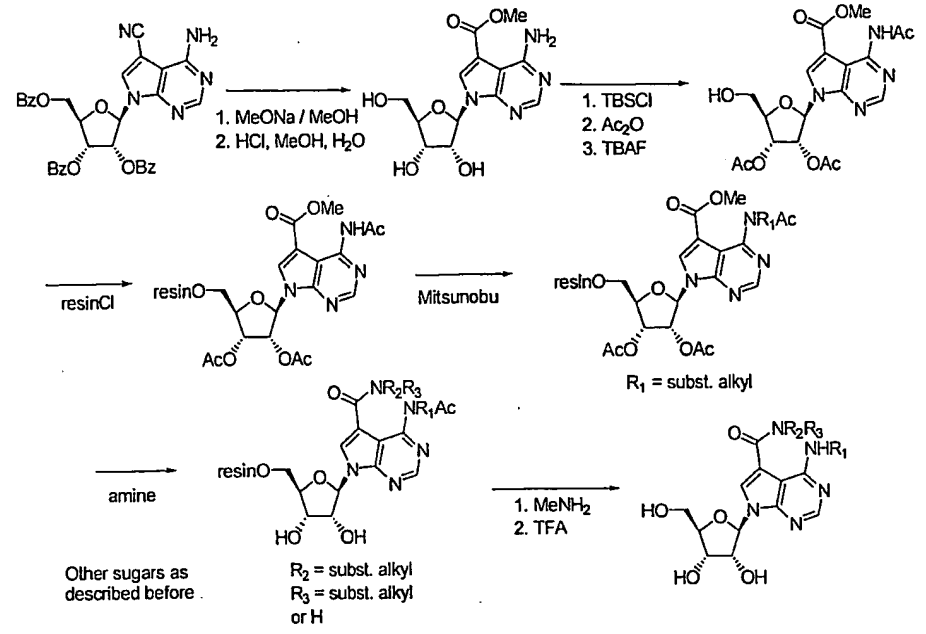
Alternatively, 7-deazapurine/toyocamycin libraries may be prepared following a procedure as shown in **Scheme 4B** below, in which the cyano group in a protected 7-deaza-7-cyano-adenosine is hydrolyzed to generate a carboxylic acid methyl ester, the hydroxyl groups in the sugar and the amino group in the heterocyclic base are protected, and the nucleoside is coupled to a resin in a similar sequence of reactions as described above. A first set of reagents is then introduced to the heterocyclic base using the amino group in a Mitsunobu reaction, and

the carboxylic ester group is subsequently reacted with a substituted or unsubstituted amine to yield the final products after deprotection and cleavage from the resin.

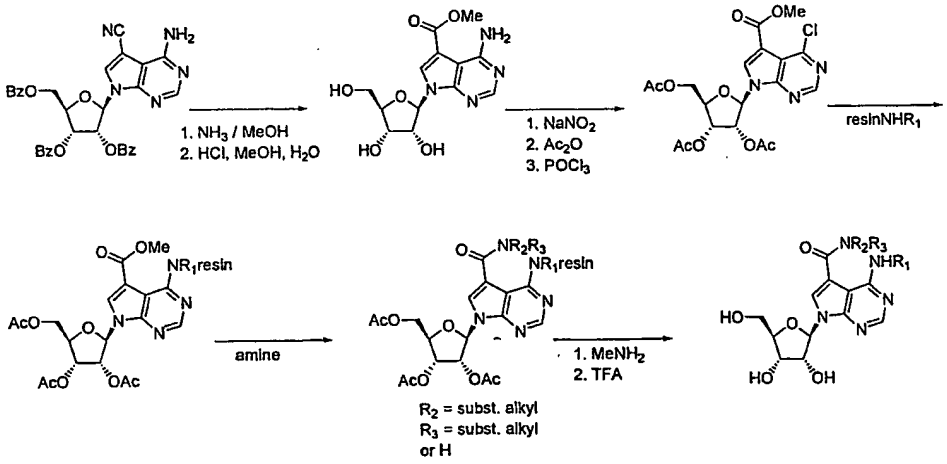
Another alternative is shown in **Scheme 4C** below, in which the cyano group in a protected 7-deaza-7-cyano-adenosine is hydrolyzed to generate a carboxylic acid methyl ester, the amino group in the pyrimidine ring is replaced by a chloro atome and the hydroxyl groups in the sugar are protected. The nucleoside is coupled to a resin already incorporating a substituted amine, and the carboxylic ester group is subsequently reacted with a substituted or unsubstituted amine to yield the final products after deprotection and cleavage from the resin. The same scheme is applicable without modification of the cyano group.



Scheme 4A

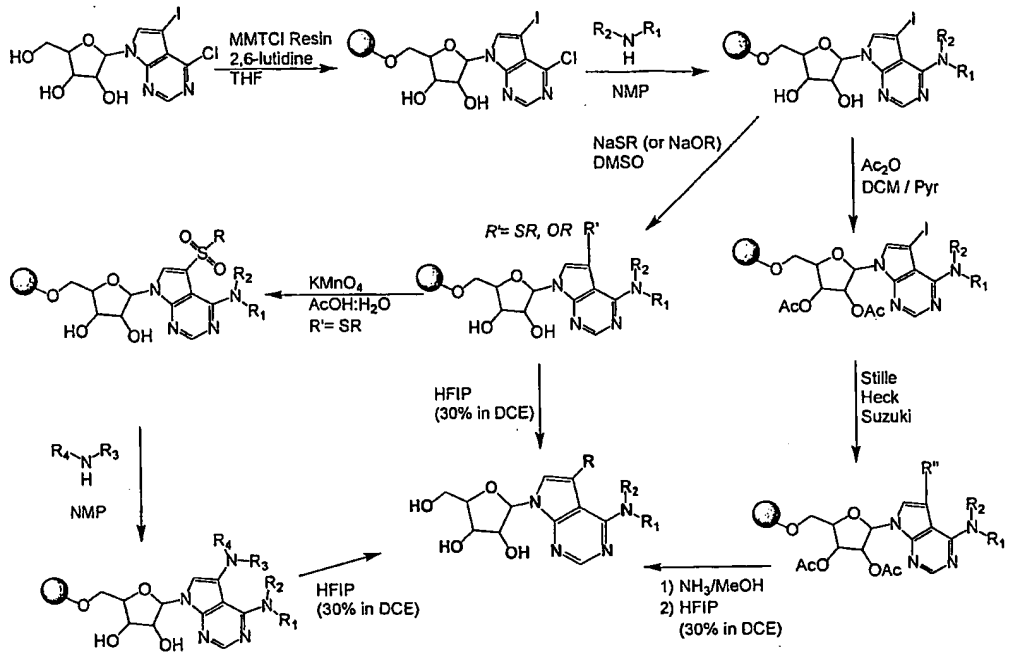


Scheme 4B



Scheme 4C

In still further alternative aspects, a 7-deazapurine library is produced following a general synthetic scheme as outlined in **Scheme 4D** below. Here, a dihalogenated 7-deazapurine is covalently coupled to a resin and is subsequently reacted with a first series of reagents (here: substituted amine) to generate a first set of products. In a further step, the second halogen is reacted with a first set of reagents in a Suzuki, Stille, or Heck reaction to yield the corresponding 7-substituted 7-deazaadenosine derivatives or the second halogen is exchanged with a leaving group, which is in turn replaced by a second set of substituents.



Scheme 4D

With respect to the sugar portions in the above-described library approaches, it should be appreciated that suitable sugars need not be limited to a D-ribofuranose, and numerous alternative sugar and sugar analogs are contemplated suitable for use herein. Particularly preferred alternative sugar and sugar analogs include a substituted ribofuranose, a carbocyclic ring system, and an arabinose or a lyxose, wherein the sugar is in a D-configuration or in an L-configuration. However, various other sugar and sugar analogs are also appropriate (see above). Consequently, the same considerations as described above apply with respect to the protecting groups and the solid phase.

Synthesis of 7-deaza-7-cyano-8-bromoadenosine is well known in the art and an exemplary synthesis is described in the Journal of the American Chemical Society 1968;90:524-526. Alternatively, 7-deaza-7-cyano-8-bromoadenosine can be prepared from 6-bromo-4-chloropyrrolo[2,3-d]pyrimidine-5-carbonitrile following substantially a procedure as described in the Journal of the American Chemical Society 1969;91:2102-2108.

With respect to the first set of reagents for Scheme 4A, it is contemplated that all reagents are suitable that will react in a Suzuki, Stille, or Heck reaction with the 8-position to replace the bromine with a saturated or unsaturated hydrocarbon, and preferably an alkyl, alkenyl, alkynyl, or aryl (all of which may be substituted with one or more substituents).

Consequently, where the reaction comprises a Heck reaction (coupling of a halogenide with an olefine with Pd(0) as catalyst), suitable first reagents may include all R-CH2=CH2, wherein R is alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; R_1 is selected from the group consisting of hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl. Likewise, where the reaction comprises a Stille reaction (coupling of a halogenide with an tin-organic compound with Pd as catalyst), suitable first reagents include $RSnR'_3$, wherein R is defined as above. Similarly, where the reaction is a Suzuki reaction (R-Br coupled to a boronic acid R'-$B(OH)_2$ with Pd-catalyst to generate R-R'), suitable first reagents include various boronic acids comprising an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl.

On the other hand, where the starting product has an H in the 8-position, it is contemplated that the 8-position remains unreacted throughout the library construction. Numerous reagents for all of the above-referenced reactions are commercially available, and it is contemplated that all of such reagents are suitable for use herein. Moreover, where such reagents are not commercially available, it should be appreciated that all of such reagents can readily be prepared without undue experimentation following simple reaction procedures as described in Advanced Organic Chemistry: Structure and Mechanisms (Part A) by Francis A. Carey, Richard J. Sundberg; Plenum Pub Corp; ISBN: 0306462435; or Advanced Organic Chemistry : Reactions and Synthesis (Part B) by Francis Carey, Richard J. Sundberg; Plenum Pub Corp; ISBN: 0306434571, or Compendium of Organic Synthetic Methods, Volume 9, by Michael B. Smith, John Wiley & Sons; ISBN: 0471145793.

With respect to the second set of reagents for Scheme 4A it is contemplated that all reagents suitable for a Mitsunobu reaction are considered appropriate for use herein. Consequently, particularly preferred reagents include various alcohols R-OH, wherein R is defined as in the fist set of reagents above. The subsequent reaction of the ester with an amine is preferably an aminolysis of the ester, and preferred substrates have a general structure of NR'R", wherein R' and R" are independently a substituted or unsubstituted alkyl, aryl, alkaryl, alkenyl or alkynyl.

Similarly, synthesis of 7-deaza-7-cyano-adenosine is well known in the art and an exemplary synthesis is described in the Journal of the American Chemical Society

1968;90:524-526. Alternatively, 7-deaza-7-cyano-8-bromoadenosine can be prepared from 6-bromo-4-chloropyrrolo[2,3-d]pyrimidine-5-carbonitrile substantially following a procedure as described in the Journal of the American Chemical Society 1969;91:2102-2108. With respect to the first set of reagents for Scheme 4B, it is contemplated that all reagents are suitable that will react in a Mitsunobu reaction with the NHAc group in the heterocyclic base (*supra*). Likewise, preferred second sets of reagents include all amine reagents that will react with the ester of the heterocyclic base in an aminolysis reaction. Thus, preferred second sets of substrates will have a general structure of NR'R", wherein R' and R" are independently a substituted or unsubstituted alkyl, aryl, alkaryl, alkenyl or alkynyl.

With respect to the first set of reagents for Scheme 4C, it is contemplated that the resin used can be prepared using procedures similar to those described in Journal of Organic Chemistry 1998;63:5300-5301 and Tetrahedron Letters 2001;42:2771-2773. Likewise, preferred second sets of reagents include all amine reagents that will react with the ester of the heterocyclic base in an aminolysis reaction. Thus, preferred second sets of substrates will have a general structure of NR'R", wherein R' and R" are independently a substituted or unsubstituted alkyl, aryl, alkaryl, alkenyl or alkynyl.

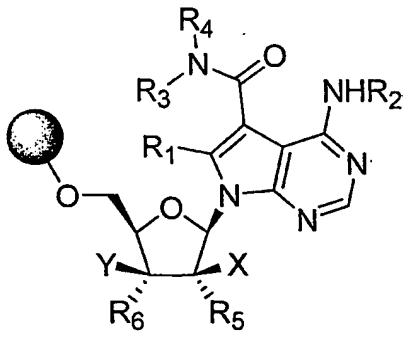
With respect to the dihalogenated 7-deazapurine in Scheme 4D, it is contemplated that various dihalogenated 7-deazapurines are commercially available. However, where particular dihalogenated heterocyclic bases are not commercially available, it is contemplated that such bases can be produced using procedures similar to those described in Journal of Heterocyclic Chemistry 1969;6:215-221.

With respect to the first set of reagents in scheme 4D, it is contemplated that all primary amines (and in some cases secondary amines) are considered suitable for use herein, and particularly preferred amines have a structure of R-NH_2, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl. Preferred second sets of reagents include all reagents that can be used to replace a leaving group in the 7-position of the deazapurine, and may therefore include R-OH, R-SH, Grignard reagents, etc.

While in all contemplated 7-deazapurine/toyocamycin libraries preferred sugars include pentose sugars (and especially ribofuranose), various alternative sugars are also contemplated

and particularly include sugars in which at least one of the C_2' and C_3' hydroxyl groups has been replaced with a non-hydroxyl substituent (*e.g.*, N_3, halogen, etc.). Still further contemplated sugars include substituents in C2' and C3' position selected from the group of OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl. Therefore, the type of protecting group (where applicable) and coupling of protecting groups may vary considerably, and all known protecting groups and coupling mechanisms are considered suitable for use herein (*supra*). Similarly, the solid phase need not be limited to a particular solid phase, and all previously contemplated protecting groups (*supra*) are deemed appropriate.

Consequently, a 7-deazapurine/toyocamycin library may comprise a plurality of library compounds according to Formula 4A, wherein a first compound of the plurality of library compounds has a first set of substituents X, Y, R_1, R_2, R_3, R_4, R_5, and R_6, wherein a second compound of the plurality of compounds has a second set of substituents X, Y, R_1, R_2, R_3, R_4, R_5, and R_6

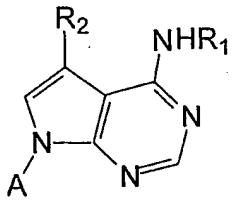


Formula 4A

wherein ● comprises a solid phase, and wherein R_5, R_6, X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, HNR, and R, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; R_1 is selected from the group consisting of hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl; and wherein R_2, R_3, and R_4 are independently an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, or a substituted alkynyl and wherein not all of the substituents R_1, R_2, R_3, and R_4 in the first set are the same as the substituents R_1, R_2, R_3, and R_4 in the second set.

In preferred libraries, X and Y are independently selected from the group consisting of H, Halogen, OR, SH, SR, R and HNR, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl, and it is especially contemplated that R_1 is hydrogen in such libraries.

Thus, contemplated compounds may have a structure according to Formula 4B



Formula 4B

wherein A is a sugar, and R_1 is selected from the group consisting of hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl, COR, CONHR, CH_2NHR; and wherein R_2 is R_1, OR_1, or SR_1, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl.

In especially preferred compounds according to Formula 4B, the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, wherein the sugar is in a D-configuration or in an L-configuration. In further preferred aspects, contemplated compounds include a ribofuranose as a sugar portion, and R_2 is OR_1 or SR_1, and/or R_1 is hydrogen and R_2 is OR or SR, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl.

Uses of contemplated libraries and compounds

In one preferred aspect, it is contemplated that the libraries according to the inventive subject matter may be used to facilitate structure-activity analysis of nucleoside-type compounds. For example, where it is known that an enzyme employs a nucleoside as substrate/co-substrate, and where an inhibitor or alternative substrate for the enzyme is desired, contemplated libraries will provide a researcher with rapid information on the impact of a particular substituent in a particular position of the library compound.

In a further example, it is contemplated that libraries according to the inventive subject matter will exhibit a significant source of revenue for a seller since in most cases purchase of a library of nucleosides, nucleoside analogs, nucleotides, and/or nucleotide analogs will be less costly to a user than individual synthesis of these compounds.

In yet another example, the library compounds may serve as *in vitro* and/or *in vivo* substrates or inhibitors with particularly desirable physicochemical and/or biological properties. Among other uses, the library compounds may act as inhibitors of DNA and/or RNA for various nucleoside-using enzymes, and especially polymerases, reverse transcriptases, and ligases. Therefore, contemplated nucleosides will exhibit particular usefulness as *in vitro* and/or *in vivo* antiviral agents, antineoplastic agents, or immunomodulatory agents. Still further, it is contemplated that nucleosides according to the inventive subject matter may be incorporated into oligo- or polynucleotides, which will then exhibit altered hybridization characteristics with single or double stranded DNA *in vitro* and *in vivo*.

Particularly contemplated antiviral activities include at least partial reduction of viral titers of respiratory syncytial virus (RSV), hepatitis B virus (HBV), hepatitis C virus (HCV), herpes simplex type 1 and 2, herpes genitalis, herpes keratitis, herpes encephalitis, herpes zoster, human immunodeficiency virus (HIV), influenza A virus, Hanta virus (hemorrhagic fever), human papilloma virus (HPV), and measles virus. Especially contemplated immunomodulatory activity includes at least partial reduction of clinical symptoms and signs in arthritis, psoriasis, inflammatory bowel disease, juvenile diabetes, lupus, multiple sclerosis, gout and gouty arthritis, rheumatoid arthritis, rejection of transplantation, giant cell arteritis, allergy and asthma, but also modulation of some portion of a mammal's immune system, and especially modulation of cytokine profiles of Type 1 and Type 2. Where modulation of Type 1 and Type 2 cytokines occurs, it is contemplated that the modulation may include suppression of both Type 1 and Type 2, suppression of Type 1 and stimulation of Type 2, or suppression of Type 2 and stimulation of Type 1.

Where contemplated nucleosides are administered in a pharmacological composition, it is contemplated that suitable nucleosides can be formulated in admixture with a pharmaceutically acceptable carrier. For example, contemplated nucleosides can be administered orally as pharmacologically acceptable salts, or intravenously in physiological saline solution (*e.g.*, buffered to a pH of about 7.2 to 7.5). Conventional buffers such as

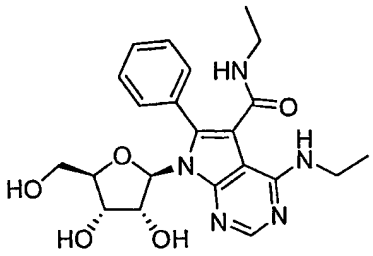
phosphates, bicarbonates or citrates can be used for this purpose. Of course, one of ordinary skill in the art may modify the formulations within the teachings of the specification to provide numerous formulations for a particular route of administration. In particular, contemplated nucleosides may be modified to render them more soluble in water or another vehicle, which for example, may be easily accomplished by minor modifications (salt formulation, esterification, *etc.*) that are well within the ordinary skill in the art. It is also well within the ordinary skill of the art to modify the route of administration and dosage regimen of a particular compound in order to manage the pharmacokinetics of the present compounds for maximum beneficial effect in a patient.

In certain pharmaceutical dosage forms, prodrug forms of contemplated nucleosides may be formed for various purposes, including reduction of toxicity, increasing the organ- or target cell specificity, etc. One of ordinary skill in the art will recognize how to readily modify the present compounds to pro-drug forms to facilitate delivery of active compounds to a target site within the host organism or patient (see above). One of ordinary skill in the art will also take advantage of favorable pharmacokinetic parameters of the pro-drug forms, where applicable, in delivering the present compounds to a targeted site within the host organism or patient to maximize the intended effect of the compound.

In addition, contemplated compounds may be administered alone or in combination with other agents for the treatment of various diseases or conditions. Combination therapies according to the present invention comprise the administration of at least one compound of the present invention or a functional derivative thereof and at least one other pharmaceutically active ingredient. The active ingredient(s) and pharmaceutically active agents may be administered separately or together and when administered separately this may occur simultaneously or separately in any order. The amounts of the active ingredient(s) and pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Among other contemplated agents for combination with contemplated compounds, it is especially preferred that such agents include interferon, and particularly IFN-alpha or IFN-beta (or fragments thereof).

Examples

4-ethylamino-5-ethylcarbamoyl-6-phenyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]- pyrimidine



a) 4-Amino-5-methoxycarbonimidoyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. Tri-*O*-benzoyl toyocamycin (12.60g, 30.19mmol) was suspended in 905 mL of methanol (30 mL/mmol) and stirred until completely dissolved. The reaction mixture was stirred at room temperature under the presence of argon. Then a 1N solution of MeONa/MeOH (11.0 mL, 11.0 mmol) was added to the reaction mixture and stirred at room temperature for 17 hrs. The reaction mixture was neutralized with a 1M solution of HCl (~10ml). The target compound was purified by silica gel chromatography (eluted with 500 ml of 8.0% MeOH/ EtoAc).

b) 4-Amino-5-methoxycarbonyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. The compound obtained in step a) (4.90g, 15.2 mmol) was suspended in a solution of MeOH (136.0 ml, 9 mL/mmol) and H_2O (379.0 mL/ mmol) stirred at 10^0 C, then a 1N solution of HCl (45.50mL, 45.4 mmol) was added. The reaction mixture was stirred at 10^0 C for ~6 hrs. 70 g of amberlite IRA-93 was added to the reaction mixture. The reaction mixture was filtered and the filtrate was concentrated which lead to a precipitate that was shown to be the target compound.

c) 4-Acetylamino-5-methoxycarbonyl-7-(2',3'-di-*O*-acetyl-5'-*tert*-butyl-dimethylsilyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. Pyridine was added to the compound obtained in step b) (4 mmol), followed by the addition of t-butylchlorodimethylsilane (1.1 eq.). The reaction mixture was stirred at room temperature for 24 h, then acetic anhydride (18 mL, 18 mmol) was added. The reaction mixture was stirred at room temperature for 24 h. Pyridine was evaporated and the residue was extracted with ethyl acetate and water. The target compound was purified by silica gel chromatography (gradient of ethyl acetate in hexane).

d) 4-Acetylamino-6-bromo-5-methoxycarbonyl-7-(2',3'-di-*O*-acetyl-5'-*tert*-butyl-dimethylsilyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. N-Bromosuccinimide (5.5g, 31 mmol) was added to a solution of compound c) (7.0g, 16 mmol) in acetonitrile (240 mL). The reaction mixture was stirred at reflux temperature for 2 h. Acetonitrile was evaporated and the residue was purified by silica gel chromatography (gradient of ethyl acetate in hexane).

e) 4-Acetylamino-5-methoxycarbonyl-6-phenyl-7-(2',3'-di-*O*-acetyl-5'-*tert*-butyl-dimethylsilyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. Tributylphenyl tin (6.5 mL, 20 mmol) was added to a solution of compound d) (5.3 g, 10 mmol) and dichlorobis (triphenylphosphine) palladium(II) ($Pd(PPh_3)_2Cl_2$) (0.7 g, 1.0 mmol) in degased *N,N*-dimethylformamide (150 mL). The reaction mixture was stirred at 85 °C for 48 h. The solvent was evaporated and the residue was purified by silica gel chromatography (gradient of ethyl acetate in hexane).

f) 4-Acetylamino-6-phenyl-5-methoxycarbonyl-7-(2',3'-di-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. Tetrabutylammonium fluoride (1.0 M in tetrahydrofuran, 11 mL) was added to a solution of compound e) (10 mmol) in tetrahydrofuran (100 mL). The reaction mixture was stirred at room temperature for 6 h. THF was evaporated and the residue was purified by silica gel chromatography (gradient of ethyl acetate in hexane).

g) 4-Acetylamino-6-phenyl-5-methoxycarbonyl-7-(5'-*O*-MMT resin-2',3'-di-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. A solution of compound f) (12 mmol) in 2,6-lutidine (1.9 mL) and anhydrous THF (36 mL) was added to a reaction vessel containing MMTCl-resin (4.5 g, 8.0 mmol). The reaction mixture was shaken at RT for 64 h. The reaction mixture was quenched by the addition of methanol (5 mL), followed by shaking for 30 min. The resin was then filtered, and washed with DMF (3×15 mL), MeOH (3×15 mL), and CH_2Cl_2 (3×15 mL). The washed resin was dried in vacuo at 45 °C overnight.

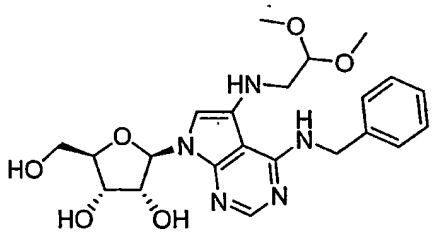
h) 4-(Acetylethyl)amino-6-phenyl-5-methoxycarbonyl-7-(5'-*O*-MMTresin-2',3'-di-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of resin f) (5 mmol) in anhydrous THF (50 mL) was added triphenylphosphine (15 mmol), ethanol (15 mmol) and DEAD (15 mmol). The reaction mixture was shaken at RT for 24 h. The reaction mixture was filtered, and washed with THF (3×15 mL), MeOH (3×15 mL), and CH_2Cl_2 (3×15 mL). The washed resin was dried in vacuo at 45 °C overnight.

i) 4-(Acetylethyl)amino-6-phenyl-5-ethylcarbamoyl-7-(5'-*O*-MMTresin-2',3'-di-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step h) above (60 mg, 70 μmol) in toluene (0.5 mL) and NMP (0.5 mL), was added ethylamine (1.4 mmol). The reaction mixture shaken for 72 h at 95 °C. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

j) 4-ethylamino-6-phenyl-5-ethylcarbamoyl-7-(5'-*O*-MMT resin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. A suspension of the resin obtained from step i) above (70 mg, 0.07 mmol) in a methylamine solution (2.0 M in methanol, 1.2 mL) was shaken at 40 °C for 2 days. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

k) 4-ethylamino-6-phenyl-5-ethylcarbamoyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To the resin obtained from step j) above (70 mg, 70 μmol) was added trifluoroacetic acid (1 mL, 1.5% in DCE). The reaction mixture was shaken for 5 min at rt. The solution was then filtered, and the filtrate evaporated to yield the desired product.

4-benzylamino-5-(2,2-dimethoxy-ethylamino)-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine



a) 4-Chloro-5-iodo-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. A solution of 4-chloro-5-iodo-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5.00 g, 12.1 mmol) in 2,6-lutidine (1.9 mL) and anhydrous THF (36 mL) was added to a reaction vessel containing MMTCl-resin (4.5 g, 8.0 mmol). The reaction mixture was shaken at RT for 64 h. The reaction mixture was quenched by the addition of methanol (5 mL), followed by shaking for 30 min. The resin was then filtered, and washed with DMF (3×15 mL), MeOH (3×15 mL), and CH_2Cl_2 (3×15 mL). The washed resin was dried in vacuo at 45 °C overnight to yield 7.25 g (85%) of the desired resin.

b) 4-Benzylamino-5-iodo-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step a) above (2.00 g, 1.97 mmol) in toluene (14.3 mL) and NMP (14.3 mL), was added benzylamine (1.57 mL, 14.3 mmol). The reaction mixture shaken for 12 h at 40 °C. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

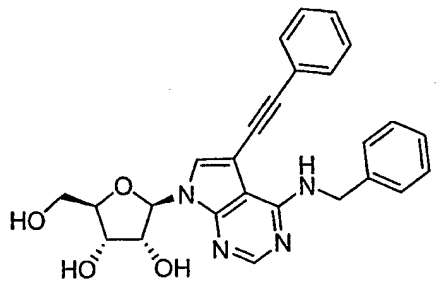
c) 4-Benzylamino-5-methylsulfanyl-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step b) above (1.8 g, 1.8 mmol) in anhydrous DMSO (5 mL) was added sodium thiomethoxide (505 mg, 7.2 mmol). The reaction mixture was shaken for 12 h at 40 °C. To the reaction mixture was added water (1 mL) followed by shaking for 30 min. The resin was filtered, washed, and dried as in b).

d) 4-Benzylamino-5-methanesulfonyl-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step c) above (1.5 mmol) in 80 % acetic acid (300 mL), was added a solution of $KMnO_4$ (1.0 g, 6 mmol) in water. The mixture was stirred for 6 h at RT. The resin was filtered, washed, and dried as in b).

e) 4-Benzylamino-5-(2,2-dimethoxy-ethylamino)-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine To a suspension of the resin obtained from step d.) above (60 mg, 60 μmol) in toluene (500 μL) and NMP (500 μL), was added amino acetaldehyde dimethyl acetal (200 μL, 1.85 mmol). The reaction mixture was shaken for 3 days at 95 °C, then filtered. The resin was filtered, washed, and dried as in b).

f) 4-Benzylamino-5-(2,2-dimethoxy-ethylamino)-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To the resin obtained from step e) above (70 mg, .07 mmol) was added hexafluoro*iso*propanol (HFIP) (1 mL, 30% in DCE). The reaction mixture was shaken for 24 h at 45 °C. The solution was then filtered, and the filtrate evaporated to yield 25.0 mg (89% for 5 steps) of product.

4-benzylamino-5-(phenylethyn-1-yl)-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine

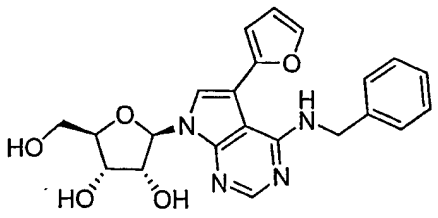


a) 4-Benzylamino-5-iodo-7-(2',3'-di-*O*-acetyl-5'-*O*-MMT resin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To an anhydrous suspension of the resin obtained in example 1b) (1.5 g, 1.5 mmol) in DCM (6 mL) and pyridine (0.56 mL, 6.8 mmol) was added acetic anhydride (0.65 mL, 6.8 mmol). The reaction mixture was shaken for 18 h at RT. MeOH (1 mL) was added, followed by shaking for 30 min. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

b) 4-Benzylamino-5-(phenylethyn-1-yl)-7-(2',3'-di-*O*-acetyl-5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step a) above (60 mg, 60 μmol) in degassed DMF (1 mL) was added dichlorobis (triphenylphosphine) palladium(II) ($Pd(PPh_3)_2Cl_2$) (2.1 mg, 3.0 μmol), triethylamine (25 μL, 0.18 mmol), and phenyl acetylene (20 μL, 0.18 mmol). The reaction mixture was heated to 90 °C and shaken for 24 h. The resin was filtered, washed and dried as in a).

c) 4-Benzylamino-5-(phenylethyn-1-yl)-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step b) above (60 mg, 60 μmol) was added methanolic ammonia (1 mL, saturated at 0 °C), and the reaction mixture was shaken for 16 h. The resin was filtered, washed and dried as in a). It was cleaved in a similar manner as in example 2f.) to yield 23.1 mg (85% for 5 steps) of compound.

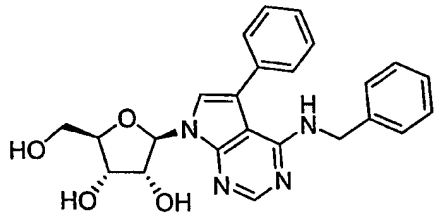
4-benzylamino-5-(furan-2-yl)-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine



a) 4-Benzylamino-5-(furan-2-yl)-7-(2',3'-di-*O*-acetyl-5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained in example 2a) (60 mg, 60 μmol) in degassed DMF (1 mL) was added dichlorobis (triphenylphosphine) palladium(II) ($Pd(PPh_3)_2Cl_2$) (2.1 mg, 3.0 μmol) and 2-(tributylstannyl)-furan (56 μL, 0.18 mmol). The reaction mixture was heated to 80 °C and shaken for 16 h. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

b) 4-Benzylamino-5-(furan-2-yl)-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step a) above (60 mg, 60 μmol) was added methanolic ammonia (1 mL, saturated at 0 °C), and the reaction mixture was shaken for 16 h. The resin was filtered, washed and dried as in a). It was cleaved in a similar manner as in example 2f) to yield 22.9 mg (91% for 5 steps) of compound.

4-benzylamino-5-phenyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine

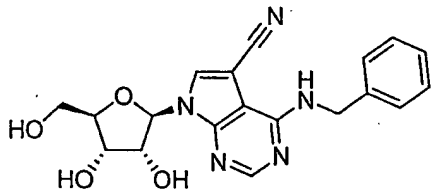


a) 4-Benzylamino-5-phenyl-7-(2',3'-di-*O*-acetyl-5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained in example 2a) (60 mg, 60 μmol) in degassed DMF (1 mL) was added 4-phenyl-boronic acid (16 mg, 0.12 mmol), K_2CO_3 (17 mg, 0.12 mmol), and $Pd(PPh_3)_2Cl_2$ (4.2 mg, 6 μmol). The reaction mixture was heated to 95 °C and shaken for 48 h. The resin was filtered and then washed with CH_2Cl_2

(3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

b) 4-Benzylamino-5-(furan-2-yl)-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step b.) above (60 mg, 60 μmol) was added methanolic ammonia (1 mL, saturated at 0 °C), and the reaction mixture was shaken for 16 h. The resin was filtered, washed and dried as in a). It was cleaved in a similar manner as in example 2f) to yield 22.5 mg (85% for 5 steps) of compound.

4-benzylamino-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine



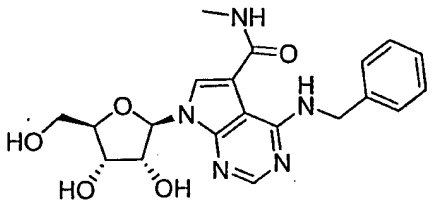
a) 4-Chloro-5-cyano-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. A solution of 4-chloro-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (3.7 g, 12.1 mmol) in 2,6-lutidine (1.9 mL) and anhydrous THF (36 mL) was added to a reaction vessel containing MMTCl-resin (4.5 g, 8.0 mmol). The reaction mixture was shaken at RT for 64 h. The reaction mixture was quenched by the addition of methanol (5 mL), followed by shaking for 30 min. The resin was then filtered, and washed with DMF (3×15 mL), MeOH (3×15 mL), and CH_2Cl_2 (3×15 mL). The washed resin was dried in vacuo at 45 °C overnight to yield 6.0 g (85%) of the desired resin.

b) 4-Benzylamino-5-cyano-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step a) above (60 mg, 70 μmol) in toluene (0.5 mL) and NMP (0.5 mL), was added benzylamine (0.16 mL, 1.4 mmol). The reaction mixture shaken for 24 h at 80 °C. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

c) 4-Benzylamino-5-cyano-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To the resin obtained from step b) above (70 mg, 70 μmol) was added hexafluoro*iso*propanol (HFIP) (1

mL, 30% in DCE). The reaction mixture was shaken for 24 h at 45 °C. The solution was then filtered, and the filtrate evaporated to yield 25.0 mg (89% for 5 steps) of product.

4-benzylamino-5-methylcarbamoyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine



a) 4-Amino-5-methoxycarbonimidoyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. Tri-*O*-benzoyl toyocamycin (12.60g, 30.19mmol) was suspended in 905 mL of methanol (30 mL/mmol) and stirred until completely dissolved. The reaction mixture was stirred at room temperature under the presence of argon. Then a 1N solution of MeONa/MeOH (11.0 mL, 11.0 mmol) was added to the reaction mixture and stirred at room temperature for 17 hrs. The reaction mixture was neutralized with a 1M solution of HCl (~10ml). The target compound was purified by silica gel chromatography (eluted with 500 ml of 8.0% MeOH/ EtoAc).

b) 4-Amino-5-methoxycarbonyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. The compound obtained in step a) (4.90g, 15.2 mmol) was suspended in a solution of MeOH (136.0 ml, 9 mL/mmol) and H_2O (379.0 mL/ mmol) stirred at 10^0 C, then a 1N solution of HCl (45.50mL, 45.4 mmol) was added. The reaction mixture was stirred at 10° C for ~6 hrs. 70 g of amberlite IRA-93 was added to the reaction mixture. The reaction mixture was filtered and the filtrate was concentrated which lead to a precipitate that was shown to be the target compound.

c) 4-oxo-5-methoxycarbonyl-7-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. The compound obtained in step b) (0.97 g, 3 mmol) was dissolved in a solution of water (60 mL) and acetic acid (8 mL), and the reaction mixture was heated at 60 °C. Sodium nitrite (2.1 g, 30 mmol) was added in three portions and the reaction mixture was stirred for 8 h. The solvent was evaporated and the residue was coevaporated with pyridine, then put in solution in the same solvent (40 mL). Acetic anhydride (12 mL, 12 mmol) was added, and the reaction mixture was stirred at room temperature for 24 h. Pyridine was evaporated and the residue was extracted with ethyl acetate and water. The target compound was purified by silica gel chromatography (gradient of ethyl acetate in hexane).

d) 4-chloro-5-methoxycarbonyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. The compound obtained in step c) (5.0 g, 11 mmol) was dissolved in phosphorus oxychloride (165 mL) and the reaction mixture was heated at reflux temperature for 1 h. It was then cooled to room temperature and pourred into ice to give a white precipitate that was filtered. The precipitate was dissolved in methanolic ammonia (300 mL) at 0 °C and left at the same temperature for 3 hours. The solvent was evaporated and the compound was precipitated in methylene chloride.

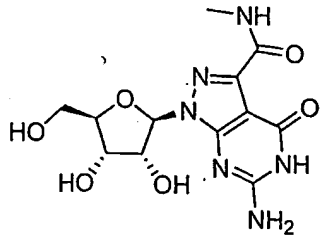
e) 4-Chloro-5-methoxycarbonyl-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. A solution of 4-chloro-5-methoxycarbonyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4.5 g, 12 mmol) in 2,6-lutidine (1.9 mL) and anhydrous THF (36 mL) was added to a reaction vessel containing MMTCl-resin (4.5 g, 8.0 mmol). The reaction mixture was shaken at RT for 64 h. The reaction mixture was quenched by the addition of methanol (5 mL), followed by shaking for 30 min. The resin was then filtered, and washed with DMF (3×15 mL), MeOH (3×15 mL), and CH_2Cl_2 (3×15 mL). The washed resin was dried in vacuo at 45 °C overnight to yield 6.7 g (85%) of the desired resin.

f) 4-Benzylamino-5-methoxycarbonyl-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To a suspension of the resin obtained from step a) above (1.8 g, 1.97 mmol) in toluene (14.3 mL) and NMP (14.3 mL), was added benzylamine (1.57 mL, 14.3 mmol). The reaction mixture shaken for 12 h at 40 °C. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

g) 4-Benzylamino-5-methylcarbamoyl-7-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. A suspension of the resin obtained from step f) above (70 mg, 0.07 mmol) in a methylamine solution (2.0 M, 1.2 mL) was heated at 95 °C for 3 days. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

h) 4-Benzylamino-5-methylcarbamoyl-7-(β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine. To the resin obtained from step g) above (70 mg, 70 μmol) was added trifluoroacetic acid (1 mL, 1.5% in DCE). The reaction mixture was shaken for 5 min at rt. The solution was then filtered, and the filtrate evaporated to yield 20 mg (75% for 5 steps) of product.

6-amino-4-oxo-3-methylcarbamoyl-1-(β-D-ribofuranosyl)pyrazolo[3,4-d]pyrimidine.



a) 6-Amino-4-oxo-3-methoxycarbonyl-1-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine. A mixture of 6-amino-4-oxo-3-methoxycarbonyl-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine (2 eq.) and MMTrCl resin (1 eq.) in pyridine was shaken for 48 h. The resin was filtered and washed with DMF, pyridine and dichloromethane. The washed resin was dried in vacuo at 45°C overnight.

b) 6-Amino-4-oxo-3-methylcarbamoyl-1-(5'-*O*-MMTresin-β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine. A suspension of the resin obtained from step a) above (70 mg, 0.07 mmol) in a methylamine solution (2.0 M, 1.2 mL) was heated at 95 °C for 3 days. The resin was filtered and then washed with CH_2Cl_2 (3×3 mL), MeOH (3×3 mL), DMF (3×3 mL) and CH_2Cl_2 (1×3 mL). The washed resin was dried in vacuo at 45°C overnight.

c) 6-Amino-4-oxo-3-methylcarbamoyl-1-(β-D-ribofuranosyl)pyrazolo[3,4-*d*]pyrimidine. To the resin obtained from step g) above (70 mg, 70 μmol) was added trifluoroacetic acid (1 mL, 1.5% in DCE). The reaction mixture was shaken for 5 min at rt. The solution was then filtered, and the filtrate evaporated to yield 20 mg (75% for 5 steps) of product.

By appropriate selection of suitable amines and specific reactants to provide the desired carbon-carbon coupling at the 5-position of the pyrrolopyrimidine, other compounds of the invention may be prepared according to the procedures described in the foregoing examples. Representative examples of reactants for substituted pyrrolopyrimidine nucleoside derivatives are set forth below:

Contemplated Reagents for Heck Reaction

2-ethynylpyridine, 5-phenyl-1-pentyne, 4-(tert-butyl)phenylacetylene, phenylacetylene, 3-dibutylamino-1-propyne, phenyl propargyl ether, 5-chloro-1-pentyne, 3-diethylamino-1-

propyne, 4-phenyl-1-butyne, 1-heptyne, 1-dimethylamino-2-propyne, 1-pentyne, 2-methyl-1-hexene, (triethylsilyl)acetylene, 3-phenyl-1-propyne, methyl propargyl ether, 3-cyclopentyl-1-propyne, 1-ethynylcyclohexene, 3-butyn-1-ol, styrene, vinylcyclohexane, 2-(tributylstannyl)furan, 2-(tributylstannyl)thiophene, tetraphenyltin, 3-cyclohexyl-1-propyne, 4-methoxyphenylacetylene, 4-(trifluoromethyl)phenyleneacetylene, 4-fluorophenylacetylene, 4-pentayn-1-ol, 4-methylphenylacetylene, 1-ethynylcyclopentanol, 3-methyl-1-propyne, 5-cyano-1-pentyne, cyclohexylethyne, 1-ethynylcyclohexene, 5-cyano-1-pentyne, 1-dimethylamino-2-propyne, N-methyl-N-propargylbenzylamine, 2-methyl-1-buten-3-yne, cyclopentylethyne, 4-nitrophenylacetylene, phenyl propargylsulfide, 4-methyl-1-pentyne, propargyl ethylsulfide, 2-prop-2-ynyloxybenzothiazole, 4-ethoxy-1-prop-2-ynyl-1,5-dihydro-2H-pyrrol-2-one, 6-methyl-5-(2-propynyl)-2-thioxo-2,3-dihydro-4(1H)-pyrimidinone and related end-alkenes and alkynes.

Contemplated Reagents for Stille Reaction

Tetraethyltin, 2-(tributylstannyl)pyridine, tributylstannyl-4-t-butylbenzene, ethynyltri-n-butyltin, vinyltri-n-butyltin, allyltri-n-butyltin, phenylethynyltri-n-butyltin, phenyltri-n-butyltin, (2-methoxy-2-cyclohexen-1-yl)tributyltin, 5,6-dihydro-2-(tributylstannyl)-4H-pyran, tri-n-butyl(2-furanyl)tin, tri-n-butyl(2-thienyl)tin, tributyl(phenylethenyl)tin, 4-fluoro-(tri-n-butylstannyl)benzene, 5-fluoro-2-methoxy(tri-n-butylstannyl)benzene, 1-methyl-2-(tributylstannyl)-1H-pyrrole, 5-methyl-2-tributylstannylthiophene, 2-tributylstannylthiazole, 2-trybutylstannylpyrrazine, tributyl[3-(trifluoromethyl)phenyl]stannane and other related organic tin reagents.

Contemplated Reagents for Suzuki Reaction

Phenylboronic acid, 4-tolylboronic acid, 2-thiopheneboronic acid, thiophene-3-boronic acid, furan-2-boronic acid, cyclopentylboronic acid, 4-methylfuran-2-boronic acid, 3-hydroxyphenyl)boronic acid, 5-methylfuran-2-boronic acid, 3-cyanophenylboronic acid, 4-cyanophenylboronic acid, (5-fornyl-3-furanyl)boronic acid, furan-3-boronic acid and other related organic boronic acids.

Contemplated Reagents for Amine Substitution Reactions

Aminoacetaldehyde dimethyl acetal, 3-aminopropionitrile, n-butylamine, hexylamine, methylamine, 2-chloroethylamine, 2,2,2-trifluoroethylamine, ethanolamine, diethylamine,

diethylamine, n,n-dimethylethylenediamine, 1,4-diaminobutane, ethylenediamine, 3-ethoxypropylamine, 3-amino-1,2-propanediol, 2-methoxyethylamine, ethylamine, isopropylamine, n-ethylmethylamine, 2-(methylthio)ethylamine, dibutylamine, 1,3-diamino-2-propanol, dimethylamine, allylamine, cyclopentylamine, beta-alanine ethyl ester, 2-(2-aminoethyl)-1-methylpyrrolidine, 2,2-dimethyl-1,3-dioxolane-4-methanamine, tetrahydrofurfurylamine, piperidine, ethyl isonipecotate, 4-amino-1-benzylpiperidine, n-allylcyclopentylamine, cyclopropanemethylamine, 4-hydroxypiperidine, cyclopropylamine, n-(2-aminoethyl)pyrrolidine, isonipecotamide, ethyl nipecotate, ethyl nipecotate, 2-piperidinemethanol, 3-methylpiperidine, aminomethylcyclohexane, 4-piperidinopiperidine, l-prolinol, cyclohexylamine, ethyl 4-amino-1-piperidinecarboxylate, 1,4-dioxa-8-azaspiro[4.5]decane, 4-piperidone, 3-hydroxypiperidine, 4,4'-bipiperidine, trans-1,4-cyclohexanediamine, piperazine, 1-benzylpiperazine, 1-(2-pyridyl)piperazine, n-(2-hydroxyethyl)piperazine, 1-methylpiperazine, l-valinol, 4-(2-aminoethyl)morpholine, 1-(2-methoxyphenyl)piperazine, 1-(2-pyrimidyl)-piperazine, 1,3-cyclohexanebis(methylamine), l-serine methyl ester, 4,4'-methylenebis(cyclohexylamine), 1-aminoindan, hexamethyleneimine, cycloheptylamine, 4-(trifluoromethyl)benzylamine, benzylamine, 1-(3-aminopropyl)imidazole, (-)-cis-myrtanylamine, n-phenylethylenediamine, 4-amino-2,2,6,6-tetramethylpiperidine, dl-alpha-methylbenzylamine, dl-alpha-methylbenzylamine, dl-alpha-methylbenzylamine, histamine, 3,4-methylenedioxybenzylamine, exo-2-aminonorbornane, thiomorpholine, 3-bromobenzylamine, 2-aminomethylbenzimidazole, 1,2,3,4-tetrahydroisoquinoline, 1,2,3,4-tetrahydro-9h-pyrido[3,4-b]indole, 2-(2-aminoethylamino)-5-nitropyridine, 2-(aminomethyl)pyridine, 3-(aminomethyl)pyridine, thiophene-2-methylamine, 1-(2-aminoethyl)-2-imidazole, homopiperazine, 3,3-dimethylbutylamine, 2-methoxybenzylamine, 1-(2-aminoethyl)piperidine, 1-(3-aminopropyl)-2-pyrrolidinone, n-methylethylenediamine, 3-methylbenzylamine, isoamylamine, n-heptylamine, 3-butoxypropylamine, 3-isopropoxypropylamine, n-(3-aminopropyl)morpholine, n,n-diethylethylenediamine, 1,2-diaminopropane, 2-(ethylthio)ethylamine, tyramine, furfurylamine, n,n-diethyl-1,3-propanediamine, 2-amino-1-phenylethanol, 4-(aminomethyl)pyridine, 4-(aminomethyl)pyridine, 4-(aminomethyl)piperidine, 2-(2-aminoethyl)pyridine, n-benzylethylenediamine, 2-phenoxyethylamine, thiophene-2-ethylamine, 3-chloropropylamine, 1-naphthalenemethylamine, 4-methoxybenzylamine, n,n-diisopropylethylenediamine, 1,2-diamino-2-methylpropane, 2-ethylhexylamine, 1-amino-2-propanol, 5-methylfurfurylamine, n,n-dimethyl-1,3-propanediamine, n,n,2,2-tetramethyl-1,3-propanediamine, 2-

methylbutylamine, 2-ethoxybenzylamine, 1-(3-aminopropyl)-2-pipecoline, 4-methylbenzylamine, hydrazine, n,n-dimethylhydrazine, methylhydrazine, 4-aminomorpholine, n-aminopiperidine, 1-aminopyrrolidine, 3-chlorophenylhydrazine, 1-amino-4-methylpiperazine, 4-fluorophenylhydrazine, 4-methoxyphenylhydrazine, phenylhydrazine, p-tolylhydrazine , 2-hydroxyethylhydrazine, 7-chloro-4-hydrazinoquinoline, 2-hydrazinopyridine, 1-aminohomopiperidine, hydroxylamine, o-methylhydroxylamine, o-benzylhydroxylamine, 3-(trifluoromethyl)benzylamine, 2-aminobenzotrifluoride, 3-aminobenzotrifluoride, 1,2-diphenylethylamine, n1,n1-dimethyl-1,2-propanediamine, 2-phenyl-propylamine, cyclobutylamine, isobutylamine, 4-aminobenzotrifluoride, 5-amino-2-methoxypyridine, 2-(trifluoromethyl)benzylamine, 2-amino-6-fluorobenzothiazole, 2-amino-5-ethyl-1,3,4-thiadiazole, 2,2-diphenylethylamine, aniline, ammonia, 4-(4-methylpiperazino)aniline, propyleneimine, pyrrolidine, n-methylcyclohexylamine, n-ethylcyclohexylamine, morpholine, n-propylcyclopropanemethylamine, 1-phenylpiperazine, allylcyclohexylamine, 1-methyl-4-(methylamino)piperidine, 2-amino-5-(4-nitrophenylsulfonyl)-thiazole, 2-amino-4-methylpyridine, 2-amino-5-methylpyridine, 4-amino-2,6-dimethoxypyrimidine, 2-amino-4,6-dimethylpyridine, 3-(methylmercapto)aniline, 2-amino-6-methylpyridine, 3-aminobenzamide, 2-aminopyridine, 2,6-diaminopyridine, 2-amino-4,6-dimethylpyrimidine, 3-aminopyridine, 2-aminopyrimidine, 3,4,5-trimethoxyaniline, 4-aminopyridine, 3,4-dimethoxyaniline, 4-methylcyclohexylamine, phenethylamine, 3-methoxypropylamine, 4-phenylbutylamine, 1,2,3,4-tetrahydro-1-naphthylamine, tert-amylamine, 2-aminooctane, 3-methoxybenzylamine, 2-methylbenzylamine, 1-phenylethylamine, l-(-)-alpha-methylbenzylamine, 2-(4-fluorophenyl)ethylamine, 1,3-dimethylbutylamine, 2-(1-cyclohexenyl)ethylamine, 2,3-dimethylcyclohexylamine, 1,2-dimethylpropylamine, 3-aminopentane, 2-fluorophenethylamine, alpha-ethylbenzylamine, alpha-ethylbenzylamine, 3-fluorophenethylamine, 3-fluorobenzylamine, 1-(4-fluorophenyl)ethylamine, 2-methoxyisopropylamine, 2-methoxyisopropylamine, (+/-)-2-amino-1-butanol, (+/-)-2-amino-1-butanol, 2-aminoheptane, dl-2-amino-1-propanol, dl-2-amino-3-methyl-1-butanol, dl-2-amino-3-methyl-1-butanol, (r)-(-)-2-amino-1-butanol, 4-amino-1-butanol, 3-amino-1-propanol, 1-methyl-3-phenylpropylamine, 1-methyl-3-phenylpropylamine, (s)-(+)-2-amino-1-butanol, 2-amino-6-methylheptane, (r)-(+)-1-phenylethylamine.

Contemplated Reagents for Mitsunobu Reaction

1-butanol, 4-nitrophenthyl alcohol, 4-chlorobenzyl alcohol, 1-propanol, 4-nitrobenzyl alcohol, 4-methoxybenzyl alcohol, 4-methylbenzyl alcohol, 2-butanol, Benzyl alcohol, 2-methyl-1-propanol, Crotyl Alcohol, 2-Norbornanemethanol, 2-Methylcyclopropane-methanol, 3-Buten-1-ol, Neopentyl Alcohol, Cyclohexylmethanol, 3-methylcyclopentanol, 3-methyl-2-buten-1-ol, Cyclopentanemethanol, 3-methyl-3-buten-1-ol, 4-methyl-1-pentanol, 4-methylcyclohexanol, 3-cyclohexene-1-methanol, 3-methyl-2-cyclohexen-1-ol, Piperonyl alcohol, Cinnamyl Alcohol, Tetrahydrofurfuryl alcohol, Ethanol, Cyclopropyl carbinol, 1-methyl-3-piperidinemethanol, Decahydro-2-napthol, 9-Decen-1-ol, 3-cyclopentyl-1-propanol, 1-methyl-2-pyrrolidineeethanol, 3-methylbenzyl alcohol, 3-fluorobenzyl alcohol, Methanol, Cycohexanol, 3-methoxybenzyl alcohol, 4-(trifluoromethyl)benzyl alcohol, 2-propanol, 2-chloro-2-propen-1-ol, 2-chlorobenzyl alcohol, 4-fluorobenzyl alcohol, 3-chlorobenzyl alcohol, 3-(trifluoromethyl)benzyl alcohol, 2-(trifluoromethyl)benzyl alcohol, Chrysanthemyl alcohol, 2-chloroethanol, 3-Methyl-1-butanol, α,α,α-Trifluoro-*p*-cresol, 3-Fluorophenol, α,α,α-Trifluoro-*m*-cresol, 4-fluorophenol, 5-Indanol, 1-Napthol, 7-Methoxy-2-napthol, 4-Phenoxyphenol, 4-Phenylphenol, 4-Cyclopentylphenol, 4-(Trifluoromethoxy)-phenol, (R)-(-)-2-chloropropan-1-ol, 3-Phenoxybenzyl alcohol, 4-isopropylbenzyl alcohol, 4-ethoxybenzyl alcohol, 3,4-dimethoxybenzyl alcohol, 3,5-dimethylbenzyl alcohol, 4-benzyloxybenzyl alcohol, Phenethyl alcohol, Trans-2-methyl-3-phenyl-2-propen-1-ol, 2-phenoxyethanol, 2-benzyloxyethanol, 1-pentanol, 3,3,-dimethyl-1-butanol, 3-pentanol, Cis-2-penten-1-ol, Cyclobutanemethanol, 3-methylphenethyl alcohol, 2-cyclohexylethanol, Cyclopentanol, Allyl Alcohol.

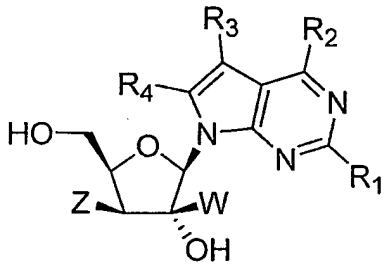
Thus, specific embodiments and applications of substituted deazapurine nucleoside libraries and compounds have been disclosed. It should be apparent, however, to those skilled in the art that many more modifications besides those already described are possible without departing from the inventive concepts herein. The inventive subject matter, therefore, is not to be restricted except in the spirit of the appended claims. Moreover, in interpreting both the specification and the claims, all terms should be interpreted in the broadest possible manner consistent with the context. In particular, the terms "comprises" and "comprising" should be interpreted as referring to elements, components, or steps in a non-exclusive manner, indicating

that the referenced elements, components, or steps may be present, or utilized, or combined with other elements, components, or steps that are not expressly referenced.

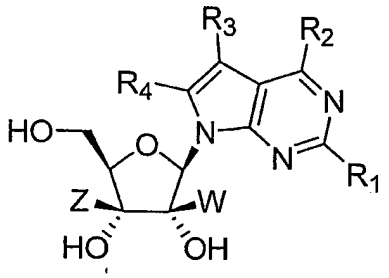
CLAIMS

What is claimed is:

1. A compound according to Formula 1A or Formula 1B



Formula 1A



Formula 1B

wherein W and Z are independently hydrogen, N_3, NH_2, OH, SH, R, or NHR wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; and

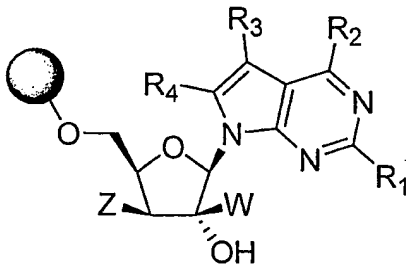
wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Halogen, NH_2, NHR', R', CN, $CONH_2$, N_3, NH_2, and CH_2CN, wherein R' is selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, and an unsubstituted aryl.

2. The compound of claim 1 wherein Z is H and W is methyl.

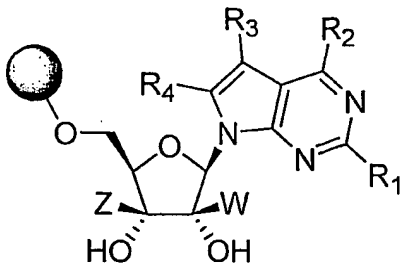
3. The compound of claim 1 wherein R_1, R_3, and R_4 are independently NHR', wherein R' is selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, and an unsubstituted aryl.

4. The compound of claim 1 wherein R_4 is halogen.

5. A plurality of compounds according to Formula 1C or Formula 1D wherein a first compound of the plurality of compounds has a first set of substituents W, Z, R_1, R_2, R_3, and R_4, wherein a second compound of the plurality of compounds has a second set of substituents W, Z, R_1, R_2, R_3, and R_4



Formula 1C



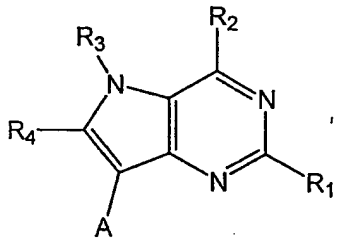
Formula 1D

wherein W and Z are independently hydrogen, N_3, NH_2, OH, SH, R, or NHR wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl; and

wherein R_1, R_2, R_3, and R_4 are independently selected from the group consisting of H, Halogen, NH_2, NHR', R', CN, $CONH_2$, N_3, NH_2, and CH_2CN, wherein R' is selected from the group consisting of a substituted alkyl, an unsubstituted alkyl, a substituted aryl, and an unsubstituted aryl.

wherein ● comprises a solid phase, and wherein not all of the substituents W, Z, R_1, R_2, R_3, and R_4 in the first set are the same as the substituents W, Z, R_1, R_2, R_3, and R_4 in the second set.

6. A compound according to Formula 2A



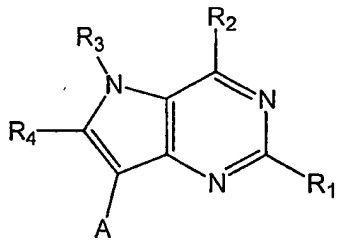
Formula 2A

wherein A is a sugar, R_1 is CHR', NHNHR', NH_2, or NHR', R_2 is SR', OR', NHR', NHNHR', CH_2CH_2NHR', or C(O)R', and wherein R_3 and R_4 are independently R', wherein R' is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl.

7. The compound of claim 6 wherein the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, and wherein the sugar is in a D-configuration or in an L-configuration.

8. The compound of claim 7 wherein R_1 is NHNHR' or NHR', R_2 is NHR', NHNHR', or CH_2CH_2NHR', and wherein R_3 and R_4 are independently R', wherein R' is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl.

9. A plurality of compounds according to Formula 2B wherein a first compound of the plurality of compounds has a first set of substituents A, R_1, R_2, R_3, and R_4, wherein a second compound of the plurality of compounds has a second set of substituents A, R_1, R_2, R_3, and R_4;



Formula 2B

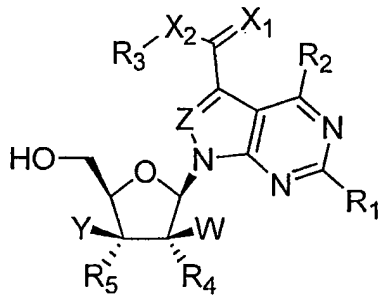
wherein A is a protected sugar that is covalently bound to a solid phase or an unprotected sugar that is covalently bound to a solid phase;

R_1 is CHR', NHNHR', NH_2, or NHR', R_2 is SR', OR', NHR', NHNHR', CH_2CH_2NHR', or C(O)R', and wherein R_3 and R_4 are independently R', wherein R' is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl; and

wherein not all of the substituents A, R_1, R_2, R_3, and R_4 in the first set are the same as the substituents A, R_1, R_2, R_3, and R_4 in the second set.

10. The plurality of compounds of claim 9 wherein the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, and wherein the sugar is in a D-configuration or in an L-configuration.

11. A compound according to Formula 3



Formula 3

wherein X_1 is NH, NR, O, S, or ONH_2; X_2 is O, S, NH, NHNH, or NR; Z is CH or N;

Y and W are independently OH, halogen, alkyl, alkenyl, alkynyl;

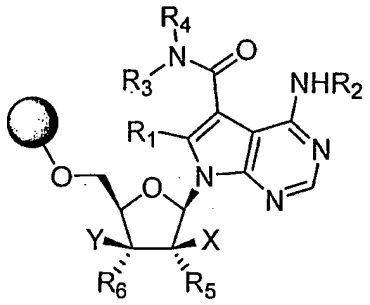
R_1 and R_2 are independently selected from the group consisting of hydrogen, halogen, OH, OR, SH, SR, NH_2, NHR and alkyl, wherein R, and R_3 are independently selected from the group consisting of hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl; and

R_4 and R_5 are independently selected from the group consisting of hydrogen, halogen, OH, OR, SH, SR, and alkyl.

12. The compound of claim 11 wherein R_4 and R_5 are OH, X_2 is O, S, or ONH, Z is CH or N, R_1 is NHCOR, $NHSO_2R$, or NHNHCOR, R_2 is OH, and wherein W and Y are independently selected from the group consisting of hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an aryl, and a substituted aryl.

13. The compound of claim 12 wherein Z is N.

14. A plurality of compounds according to Formula 4, wherein a first compound of the plurality of compounds has a first set of substituents X, Y, R_1, R_2, R_3, R_4, R_5, and R_6, wherein a second compound of the plurality of compounds has a second set of substituents X, Y, R_1, R_2, R_3, R_4, R_5, and R_6



Formula 4

wherein ● comprises a solid phase, and wherein R_5, R_6, X and Y are independently selected from the group consisting of H, OH, Halogen, OR, SH, SR, R and HNR, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl;

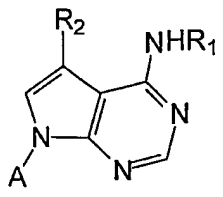
R_1 is selected from the group consisting of hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl; and

wherein R_2, R_3, and R_4 are independently a substituted or unsubstituted alkyl, and wherein not all of the substituents X, Y, R_1, R_2, R_3, R_4, R_5, and R_6 in the first set are the same as the substituents X, Y, R_1, R_2, R_3, R_4, R_5, and R_6 in the second set.

15. The plurality of compounds according to claim 14 wherein X and Y are independently selected from the group consisting of H, Halogen, OR, SH, SR, R and HNR, and wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, a substituted alkynyl, an aryl, or a substituted aryl.

16. The plurality of compounds according to claim 15 wherein R_1 is hydrogen.

17. A compound according to Formula 5



Formula 5

wherein A is a sugar, and R_1 is selected from the group consisting of hydrogen, an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl, COR, CONHR, CH_2NHR; and

R_2 is R_1, OR_1, or SR_1, wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl.

18. The compound according to claim 17 wherein the sugar is selected from the group consisting of a ribofuranose, a substituted ribofuranose, a carbocyclic ring system, and an arabinose, wherein the sugar is in a D-configuration or in an L-configuration.

19. The compound according to claim 18 wherein the sugar comprises a ribofuranose and wherein R_2 is OR_1 or SR_1.

20. The compound according to claim 18 wherein R_1 is hydrogen, R_2 is OR or SR, and wherein R is an alkyl, a substituted alkyl, an alkenyl, a substituted alkenyl, an alkynyl, and a substituted alkynyl, an aryl and a substituted aryl.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/40416

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07H 19/00, 19/22
US CL : 536/27.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 536/27.1, 18.7, 22.1, 27.13, 28.6, 29.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
REGISTRY, CAPLUS, USPATFULL, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	IIMORI et al. 2'-C, -3'-C- and 5'-C-Methylsangivamycins: Conformational Lock With THe Methyl Group. Tetrahedron Letters. 1991, Vol. 32, nO. 49, pages 7273-7276, especially page 7273.	1-5, 11-20
Y	MURAI et al. A Synthesis and an X-Ray Analysis of 2'-C-, 3'-C- and 5'-C-Methylsangivamycins. Heterocycles. 1992, Vol. 33, No. 1, pages 391-404, especially pages 391-392.	1-5 and 11-20
Y	US 4,584,369 (KLEIN et al.) 22 April 1986 (22.04.1986), columns 2-3.	6-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search
19 March 2003 (19.03.2003)

Date of mailing of the international search report
03 APR 2003

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Form PCT/ISA/210 (second sheet) (July 1998)